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SURGERY

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Society for Vascular Surgery

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SURGERY

VOL. 26 JULY, 1949 No. 1

Original Communications

Society for Vascular Surgery

THE PRESENT EVALUATION OF THE PROPHYLAXIS AND TREATMENT OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM

ARTHUR W. ALLEN, M.D.,* BOSTON, MASS.

THERE have been so many epoch-making contributions to vascular surgery by members of this Society that I recognize, with due humility, the honor you have conferred upon me by making me your president this year. My interest in lesions of vascular origin has been widespread and still I am fully aware that there are many among you whose accomplishments in this field have been far more significant than mine. It is my hope and expectation that this Society will stimulate research and interest in this important branch of surgery. There are many controversial subjects to be clarified in the better understood disorders of the vascular system and there remain many new approaches to the problems as yet beyond the present scope of therapy.

That I have chosen the subject of thrombosis and embolism for this presentation is twofold in origin. The chief reason is that in later years my main interest in vascular lesions has been along these lines, and I therefore freely admit what you already know, that is, that my competence to discuss any other problem in this field would be questionable. The second reason is that I believe it is appropriate to bring our present data together with a critical eye on the results obtained up to this time. Considering the effort expended in various clinics for the prevention and treatment of thrombosis and nonfatal pulmonary embolism, one is at times somewhat doubtful of its comparative value. Statistically it seems possible for the pathologist to show, quite clearly, that just as many deaths from pulmonary embolism occur now as was evident ten years ago.[1] On the other hand, many clinicians can demonstrate with equal clarity that hundreds of patients are living, as a result of their efforts, who would have been dead from embolism if left untreated.

William H. Welch, the pathologist, made early and notable contributions in describing the way and manner in which thrombosis in the veins occurs. It is probable that he interested the physiologist, W. H. Howell, in the problem

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*Consultant in Surgery, Massachusetts General Hospital, Boston; President, American College of Surgeons.

and it was the latter who completed research on the chain of substances and sequence of events in the clotting mechanism of the blood. It is also to McLean[2] working with Howell[3] that we owe the discovery of heparin and its antagonistic effect on clot formation; also, the suggestion that this substance if synthesized or purified might be valuable in the prevention of the pathologic phase of thrombosis. Charles and Scott[4] of the Connaught Laboratories did purify this substance and its action was determined on experimental animals by Murray, Best, Jaques, and Perrett.[5] Almost simultaneously Murray and Best[6] in Toronto, and Scandinavian surgeons, notably Crafoord[7] and Zilliacus,[8] stimulated by the chemical researches of Jorpes[9] in Sweden, began using heparin in the treatment of thrombophlebitis and nonfatal pulmonary embolism. Heparin was expensive and tedious to administer but had the advantages of rapid action and an effective counter agent in protamine.[10] Several investigators have reported gratifying results from the use of this agent, and modifications in its administration have been made by Bauer[11] and Loewe and associates.[12] Reductions in deaths from pulmonary embolism by the use of this method vary from 0 to 1.6 per cent in comparative series of cases. Bauer particularly has shown that constant and intelligent vigilance of vulnerable patients offers an opportunity for early diagnosis of thrombosis. The results are more spectacular in these early treated patients since cure is more rapidly effected and the number of sudden fatal emboli without warning is reduced. Furthermore, the postphlebitic sequelae are thereby diminished.

Homans[13] was the first, in this country at least, to call attention to the possibility of preventing recurring pulmonary embolism by interruption of the deep veins of the legs. Also, to him we owe the distinction between the type of thrombosis that he termed "bland" from the usually better recognized inflammatory variety. The former causes little reaction and is difficult to diagnose but is dangerous because the clot is loosely held within the vein. Homans' work led to the common use of phlebotomy, thrombectomy by suction, and interruption of the deep veins of the legs in the prevention and treatment of thrombosis and embolism. This method of treatment is effective, is not disabling to the patient, and is admitted by all observers to have a definite role in the proper management of this complication of illness, trauma, parturition, and postoperative convalescence. It does, on occasion, prove of value in an apparently healthy, ambulatory individual whose only complaint is repeated attacks of sudden and often transient pain within the thorax.

To Ochsner and DeBakey[14] we owe the information regarding vasospasm as an enhancing mechanism in the production of thrombosis within the veins. This led them to introduce the valuable method of treatment of thrombophlebitis by repeated procaine blocks of the lumbar sympathetics. We believe that vasospasm may well account for the increased amount of thrombophlebitis seen in cold climates as compared to warmer zones. This seems further substantiated by the incidence of this disease being at its lowest ebb during the summer and highest during the winter in New England.[15] This seasonal variation has also been noted by Crutcher and Daniel[16] in Tennessee, with the lowest incidence found to be during the Fall months in material analyzed from the Vanderbilt University Hospital.

Ochsner and DeBakey[17] have further clarified the two types of thrombosis and suggested the term phlebothrombosis to indicate the bland, loose, dangerous thrombus responsible for most of the sudden deaths from massive embolism.

Quick's[18] basic contribution on the prothrombin measurements in the blood has been found so fundamental in the proper management of patients that it deserves special mention. Chargaff, Bancroft, and Stanley-Brown,[19] using this method in a series of patients, demonstrated that all cases of postoperative thrombophlebitis observed during their period of study occurred in those individuals with a prothrombin time lower than normal. That this test was not universally adopted was due to two factors. One was that sufficient skilled laboratory technicians were lacking in most institutions. The other was that at this time no definite plan of proved specific therapy was available. Recently, Mahoney and Rice[20] have revived and somewhat simplified the routine laboratory examination of every patient in their clinic. They have shown that by this technique they can select for treatment only those patients whose prothrombin time becomes notably reduced during the first postoperative week. If it can be demonstrated that routine laboratory determinations can be carried out on all patients from a practical standpoint, many unnecessary routine precautionary measures can be avoided. I feel that in line with this type of research lies a great future in the management of this problem.

The discovery and synthesis of the inexpensive, easily administered and effective anticoagulant, Dicumarol, by Link[21] has brought about a widespread adoption of this drug by many clinicians. The excellent results in comparative groups of patients treated by this method after thrombosis has become manifest are comparable to those obtained by heparin. Notable contributions on this subject have been made by Allen and co-workers[22] at the Mayo Clinic, Evans and Dee[23] of the Lahey Clinic, and by several Scandinavian surgeons. Prophylactic use of this drug has also been stressed by Bruzelius[24] of Stockholm, Allen and associates[22] of Rochester, Minn., Smith and Mulligan[25] of Boston, and others. The dangers from hemorrhage not only in the operative site but elsewhere in the body, particularly in the brain, cannot be overemphasized. There are some patients who appear to be particularly sensitive to this drug, while others are abnormally resistant. Our present methods of determination of its effect may not be sufficiently reliable since it appears from observations that some patients apparently get some protection from it even though there is no measurable change in the prothrombin level. It is certain to us, at least at this time, that Dicumarol should never be used empirically and that accurate, frequent laboratory determinations should be made until its effect has ceased.

Perhaps we should have given priority in this discussion to the general nonspecific measures available in the prevention of thrombosis of the veins. Pool[26] was the first to call my attention to the importance of routine maneuvers for the prevention of this complication. Many of the pulmonary infarcts that are now so quickly recognized were thought to be due to other causes. Cutler[27] was one of the early clinicians to recognize the frequency of infarcts as the chief cause of postoperative chest complication. Pool thought that patients should be turned frequently in bed, that abdominal binders were a menace, and that pas-

sive and later active exercises of the legs were beneficial. To this has been added many helpful features, the most important of these being the elevation of the foot of the bed when feasible, the use of elastic leg bandages, and early postoperative walking. Such general measures can be carried out on nearly 100 per cent of the patients treated in the majority of the hospitals in this country. There are, however, many patients seen in large teaching clinics where the aged, the desperately ill, those with advanced malignancy, and the bedridden cannot avail themselves of these general measures to its full extent. For these, more specific methods of prevention of thrombosis must be considered.

It seems obvious now that we should consider the whole problem of thrombosis and embolism in two distinct categories. The first and most logical, and the one we feel that should be generally adopted, is to direct our interest primarily to the prevention of this complication. This attitude has come about because without it we cannot prevent a considerable number of sudden deaths from massive embolism in patients who give no obvious clinical manifestation that thrombosis of the veins is present. Also, there are a minority of cases where the thrombus does not originate in the leg veins, but elsewhere in the vascular system. That treatment of thrombosis and nonfatal emboli is reasonably effective by the intelligent use of femoral vein interruption, procaine sympathetic blocks, and anticoagulants is well established. It is believed, however, that in the vulnerable patients, prophylaxis has much more to commend it. It is probable that we would be definitely lacking in duty if the known, safe precautions were not adopted in suitable cases. The legal aspects of this situation must be kept in mind.

It is now my purpose to present the data on the problem under discussion from the Massachusetts General Hospital up to June, 1948. This experience is based on 2,929 patients receiving specific preventive or therapeutic measures for thrombosis. These were distributed throughout the hospital in medical and surgical wards and in the private pavilions. It is noteworthy, in spite of a very concerted interest in this subject by a majority of the staff, that we now find, at post-mortem, as high a ratio of deaths from pulmonary embolism as occurred ten years ago. This is due partly to the fact that few patients now die of shock, infection, or pneumonia and live long enough after operation to develop phlebothrombosis. Also, there has been a definite increase in the percentage of aged, desperately ill patients admitted to the hospital in the past decade as compared to previous years. The magnitude of surgical procedures has also changed. It is well known that the older the patient the greater the likelihood of thrombosis. Also, the character of the disease has a definite bearing on this complication. Patients with trauma to the lower extremities, those with abdominal malignancy, and those with cardiac decompensation are particularly vulnerable to thrombosis and embolism.

The first specific measure carried out was the use of heparin in the treatment of thrombophlebitis. This method did not give the same satisfactory results reported by Murray and Best.[6] The spectacular effect of phlebotomy, thrombectomy, and femoral vein interruption in the early cases made this the chief method of treatment for a period of years. During this time it was soon

found, if vein interruption was indicated, that a bilateral procedure should be done; also that the level of choice was the superficial femoral at its source. The apparently uninvolved vein was often found to be normal and it was interesting to see how little postoperative swelling appeared on this side as compared to the obviously involved extremity. This led to the feeling that there was justification in the use of femoral vein interruption as a prophylactic measure in vulnerable cases. Since there are two identical surgical services, it seemed logical to try prophylactic Dicumarol in small doses on one service and use the other as a control. This experience helped us learn how and when to use this drug and gave us definite proof of its value as a preventive measure.

So far phlebotomy, thrombectomy when thrombus was present at the level of the highest point of the superficial femoral vein, and interruption of the veins at this level have been performed in 1,332 patients. About one-third of these had had one or more nonlethal emboli. Approximately two-thirds of them were subjected to the procedure for positive signs of thrombosis on examination of the legs. A few were operated upon because of a slight concomitant rise in the temperature, pulse, and respirations, although these patients were symptomless. In this group, six patients succumed to further emboli. Some of these patients were treated with procaine lumbar sympathetic blocks, particularly if there was evidence of continued activity of the inflammatory process within the veins. Those who had infarcts after vein interruption were treated also with anticoagulants. A few were subjected to vena cava ligation if the emboli continued or were septic in nature. Based on previous analyses of patients with thrombosis of the leg veins, approximately 80 deaths would have been expected in this group of 1,332.

During the period covered by this study, 950 patients were selected for prophylactic superficial femoral vein interruption. These were the older age patients with lesions or infirmities that made them particularly vulnerable to thrombosis and embolism. The operation was done prior to the enforced bed rest of the chief operative procedure, during the main operation or within seventy-two hours of the convalescent period. In this group by comparative data 40 deaths would have been expected from embolism. Four of the patients did die from this cause in spite of the prophylactic procedure.

In 647 patients between the ages of 40 and 60 years, 200 mg. of Dicumarol were used within forty-eight hours of the operative procedure. If there was no evidence of elevation of prothrombin time within forty-eight hours another dose was given. In some large individuals the initial dose was 300 mg., and in some delicate and more feeble patients only 100 mg. was given. Occasionally, in a particularly resistant patient, multiple doses were used. Many of these, however, received only one dose before they became ambulatory and were considered by the danger point. In these 647 patients, the percentage of thrombosis was reduced by 80 per cent as compared to the control series. There was some definite evidence of increased bleeding tendency from intestinal suture lines and in large denuded areas such as follow combined abdominoperineal operations. No fatalities from pulmonary embolism occurred in this group of patients but two patients died of hemorrhage in the treated cases. It is fair

to say that both of these patients might have died had they not received the drug and, in one instance, there is little evidence that Dicumarol had any bearing on the subarachnoid hemorrhage occurring within fourteen hours after the administration of 200 mg. of the drug.

None of the 2,282 patients subjected to femoral vein interruption lost his life or his leg as a result of the procedure. Wound infection occurred rarely as did collections of lymph in the operative wound. The follow-up studies reveal that none of the prophylactically treated patients had vesper edema on examin tion one or more years later. In the therapeutic vein interruptions, 5 per cent had some evening swelling that was measurable and revealed slight pitting edema. Approximately 10 per cent of these patients in both the prophylactic and therapeutic group complained of night cramps in the legs if they had been unusually active during the day. The procedure did not produce varicosities of the saphenous system. Those who had varicose veins prior to femoral vein interruption were equally divided in their opinions as to whether the superficial varicosities were better or worse after the procedure. Only two patients presented varicose ulcers that had not been present before operation. No patient was disabled sufficiently to interfere with his usual occupation after femoral vein interruption.

CONCLUSIONS

1. A simple, quick laboratory procedure is needed to predict which patient needs specific efforts to prevent thrombosis and embolism. The present prothrombin activity determinations require skilled technicians and many of them, if all patients are to be evaluated in this manner.

2. A safer anticoagulant drug is desirable. Heparin is expensive and tedious to administer. Dicumarol has the disadvantage of delayed and accumulative action. It should never be used empirically. Frequent laboratory determinations of the prothrombin time are essential during its use. A long week end with laboratories closed may prove disastrous.

3. The proper use of anticoagulants will result in fewer instances of thrombosis and embolism. The contraindications to their use must be borne in mind. The dangers may outweigh the advantages with improper use.

4. Superficial femoral vein interruption when properly carried out is a safe procedure. This does not produce disabling sequelae. Its disadvantages are that the patient usually has to make an extra trip to the operating room. It does not entirely eliminate further infarcts and it fails to protect a few patients from fatal embolism.

5. Early treatment of thrombophlebitis by either anticoagulants, repeated procaine blocks of the lumbar sympathetic pathways, or superficial femoral vein interruption hastens the recovery of the disease. These methods eliminate the disabling postphlebitic edema frequently seen in patients who are allowed to recover spontaneously from thrombophlebitis.

6. It is logical that our attention should be focused on the prevention of thrombosis rather than the treatment of the disease after the process has developed. The chief reason for this attitude is that it is the only way to prevent sudden death from pulmonary embolism in symptomless phlebothrombosis.

ADDENDUM

Since delivery of this paper one year ago, therapeutic femoral vein interruption and prophylactic Dicumarol and femoral vein interruption have continued to be practiced with gratifying results. A total of 905 middle age group patients have been given Dicumarol prophylactically following operation with no fatalities from pulmonary embolism and no further fatal hemorrhages. In all, 1,500 patients have undergone femoral vein interruption as a therapeutic measure, and 7 of these have succumbed to postinterruption fatal emboli. There have been 1,078 prophylactic interruptions carried out, with 5 postinterruption deaths from embolism; 2,578 patients have been subjected to femoral vein interruptions without loss of life or limb, a result of the operative procedure.

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THE MANAGEMENT OF RECOVERY FROM VENOUS THROMBOSIS IN THE LOWER LIMBS

JOHN HOMANS, M.D., BOSTON, MASS.

THIS report is based upon a study of fifty-five cases exhibiting the quiet stage of venous thrombosis, or phlebothrombosis in the lower limbs. It was hoped to learn how the management of the immediate and remote convalescence had influenced the ultimate state of the affected leg or legs. A few patients were treated by conservative measures alone, most were subjected to some form of vein interruption, and a smaller number to anticoagulant therapy. Though many of these patients had suffered from pulmonary embolism, no attempt is made here to determine the relative lifesaving value of the various procedures, the ultimate fate of the leg being the only consideration. Well-developed obstructive thrombophlebitis is not included. I have previously discussed the late results of this disease.[1]

Before describing the results obtained, I will name some of the considerations on which they seem to depend. The first is the influence of bed rest and the management of the return to normal activity upon the course of thrombosis and its effects, and, in particular, upon secondary edema and the establishment of a permanently competent collateral venous return.

The second is the significance of a damaged or intact superficial femoral vein. Common experience indicates that, in the absence of thrombosis, surgical interruption of the vein distal to the profunda leaves no permanent trace. But the Swedish School (Bauer,[2] Zilliacus,[3] Birger[4]) maintains that thrombosis must be prevented from occupying the vein if serious aftereffects in the form of edema, induration, and ultimate ulceration in the lower leg are to be avoided. One might expect, therefore, that the successful use of anticoagulants confining the process to the lower leg would give a different result from that of surgical interruption of the superficial femoral vein under similar circumstances.

The third consideration is the significance of the communications between the superficial and deep femoral veins and those of the combined deep and superficial femoral systems with higher veins. Here the recent anatomic observations of Edwards[5] on the cadaver seem to me to be important. Edwards studied the connections, in the lower- and mid-thigh, between the superficial and profunda systems. In about 10 per cent of the thighs examined, the two systems intercommunicated so freely as practically to be one. And, in general, the profunda veins offered themselves as useful collaterals when the superficial femoral was obstructed or rendered incompetent. By contrast, the communications between the combined deep and superficial femoral vessels with the great circumflex veins of the upper thigh and the pelvic system above were found to be astonishingly few. Thus, the collaterals available when the common femoral vein is interrupted proximal to the profunda are few and small.

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A consideration to be kept in mind, but which is only very incidentally taken up here, is the ultimate patency of the deep and superficial veins directly affected by thrombosis. It is assumed that any thrombus disables the valves of a vein whether or not obstruction is so complete that it permits a lumen to be restored only by canalization. It is further assumed that a canalized vein, once valved but now valveless, is more harmful to the individual than one which remains permanently obstructed, since it can neither forward blood against gravity nor prevent excessive back pressure.

Material.—No prophylactic interruptions are included. The fifty-five cases studied were private patients usually able and willing to make use of a planned convalescence. As a rule, they had been attacked by thrombosis in everyday life rather than following operation or serious illness. In such persons one has a better opportunity to judge the extent of the thrombus before treatment is begun than in ill patients already confined to bed. Moreover, the thrombosis of ambulatory life is far more often confined to one leg (as clearly appears here) so that one is able to compare the state of the affected limb with the second one. The first patient was treated nineteen years before this report; the last, six months before.

Treatment by Physiotherapy Only.—Six legs were so treated, all for thrombosis of the unilateral, early type. Two suffered an early recurrence and were subjected to superficial femoral vein interruption. Of the other four, three report themselves as well, and one cannot be traced. These cases are of interest chiefly as showing that cures are often secured, unpredictably, by physiotherapy alone. The end results are similar to those of early disease treated by anticoagulants.

SURGICAL INTERRUPTIONS AT VARIOUS LEVELS

Interruption of the Superficial Femoral Vein (Distal to the Profunda).—For the purposes of this study, there have been 30 such interruptions on 29 patients.* These were the first operations undertaken. All but 2 patients have been seen personally or have given such a complete account of their present state that the observation can be trusted. Thrombosis was usually early and apparently confined to the lower part of the leg. In a few instances, the disease was more advanced, having passed the popliteal and invaded, without fully obstructing, the superficial femoral vein. In 1, the operation was followed by embolism, for which heparin was successfully used. In only 2 instances were both legs involved (common femoral vein interruption was performed on one of these legs). A typical case and the first one treated is the following:

*Three other cases of superficial vein interruption are not included. They illustrate failure of the operation to prevent embolism and give no information as to the subsequent state of the leg. In one, bilateral interruption for recurrent embolism was followed by fatal embolism; in a second, unilateral interruption for embolism was followed by fatal embolism (the disease was confined to the side of operation as shown by autopsy); and in a third, unilateral interruption was followed by serious embolism and required ligation of the vena cava, with recovery. These three cases are believed to represent postoperative extension of the lower-leg thrombus, by way of the deep femoral system, into the common femoral vein, by-passing the superficial femoral interruption, since in all three, no thrombus was found in the superficial femoral vein at operation. They illustrate the need of adding anticoagulant therapy to this operation, which otherwise will not only fail to halt embolism in about 10 per cent of all cases, but may actually hasten it.

A. S. F., a single woman, 43 years of age, was seen Dec. 3, 1929. As a result of a minor accident, she had suffered a "subperiosteal" fracture of the fifth metatarsal bone (left). Treatment at first was by rest in bed. On ambulation, the left ankle and lower leg swelled. On two subsequent occasions there was complete relief of edema and lameness of the calf on bed rest, with recurrence on getting about. Seven weeks after the accident, the left superficial femoral vein was ligated in continuity, and the popliteal vein was exposed but not opened or ligated. Blood flow here seemed diminished, but no thrombus was demonstrated. Postoperative treatment included elevation of the foot of the patient's bed and exercise of the leg in bed. No walking was allowed for nine days. After hospitalization for eleven days, the patient gradually returned to active life, wearing an elastic stocking and suffering no disorder of any sort. A nineteen-year follow-up shows no edema, no venous stasis, no lameness. The state of the two legs is identical.

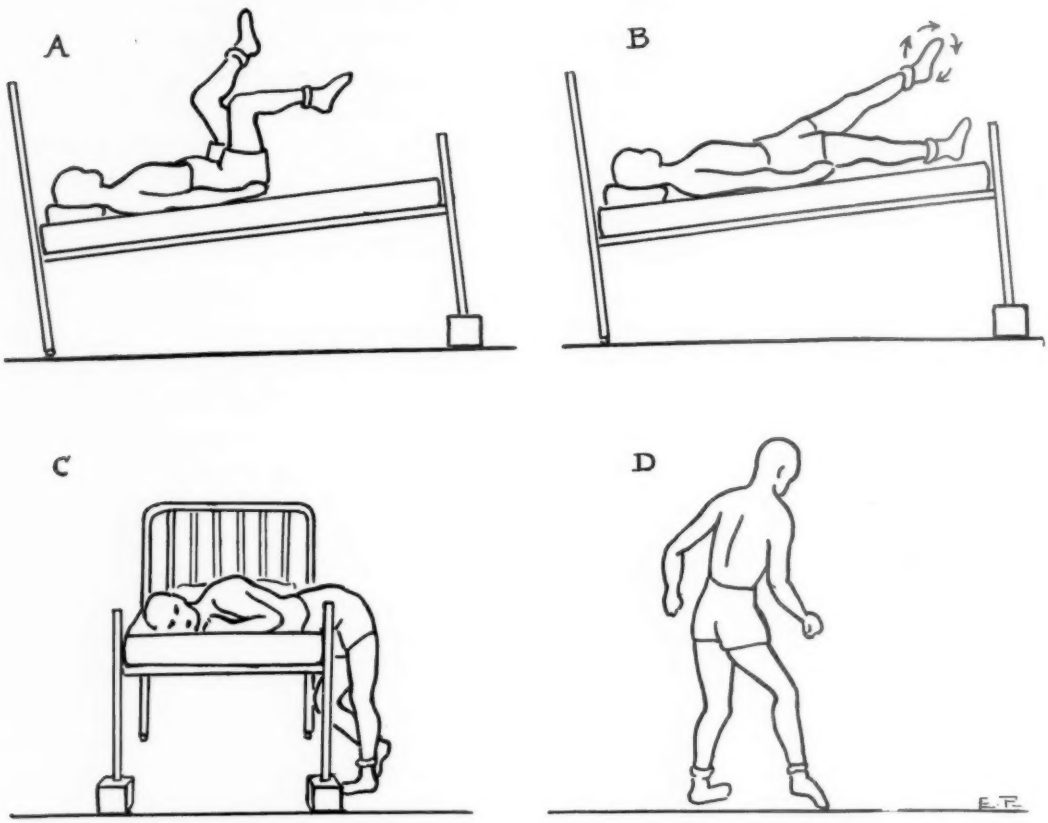

Fig. 1.—*A* and *B*, Bicycle and foot exercises in bed. *C*, Preliminary walking exercises with diminished weight-bearing and lowered venous hydrostatic pressures. *D*, Full use of the lower-leg muscles in walking.

Postoperative management of subsequent femoral vein interruption has followed a similar scheme and has included: (1) Rest in bed, elevated four inches at the foot, until all evidences of thrombosis have disappeared, usually for about a week; (2) bathroom privileges, which seem to offer sufficient "early ambulation"; (3) free exercise of the legs in bed, including bicycle movements in the elevated position; (4) light bandaging from toes to knee whenever the patient gets out of bed; (5) walking exercise without weight-bearing as shown in Fig. 1, *C* for gradually increasing periods, followed by resumption of normal

ambulation if no swelling or lameness is excited; (6) bandaging or the wearing of an elastic stocking for the first few weeks after hospitalization in the more serious cases and as an optional matter for the early ones; and (7) as a parallel precaution, as the convalescence continues, elevation of the legs above the body for brief periods during the day, to pay for periods of dependency. The plan has been to keep the venous pressure low, and especially to prevent wide variations. Obviously not all patients will pay equal attention to this system. One athletic, muscular, youngish man began playing golf within one month of the operation, and now, ten years later, after a strenuous life during the late war, shows no sign of circulatory disorder. (The thrombosis had caused recurring edema and cyanosis of the lower leg for several weeks before operation.)

Reports have been secured upon 28 of the 30 limbs treated by superficial femoral vein interruption. The results in 21 are excellent, and these include 3 combined saphenous vein interruptions. In 5 others, there is slight residual edema without complaints. In 2 others, previously existing varicose veins have recurred and progressed. Of the 2 untraced, 1 had presented a perfect result at five months; the second had stood for twelve hours a day from the start, and showed persistent edema with early skin changes a year later.

Evidently, superficial femoral vein interruption for thrombosis confined to the lower leg is not very harmful to the venous return. That it throws the superficial femoral, with its useful valves, out of function is not proved, but, in any case, experience with its use tends to lessen the validity of the Swedish contention. Following the interruption, a carefully controlled convalescence would seem to be unnecessary were it not for the occasional unpleasant postoperative reaction in the lower leg to any sort of femoral vein section. For in one or two instances, local pain, muscular irritability, and lameness have occurred on the first attempts to walk and have persisted until relieved by several days of elevation of the leg in bed and a second start. This has seemed to me to indicate a rather inflammatory type of thrombosis and extension into new vessels, that is, a failure of healing of the thrombotic process, or even an actual spread with a threat to the collateral circulation. The use of anticoagulants following the interruption should prevent any such extension, including involvement of the profunda system, and embolism from that source.

Common Femoral Vein Interruption.—I have performed few of these operations, and since they are most often used to combat embolism and relatively advanced thrombosis, unilateral interruptions are a rarity. They tend to result, probably by reason of the unsatisfactory connections of the combined superficial and deep femoral systems with higher veins, in chronic edema, venous engorgement, and postphlebitic induration and ulceration. However, they offer an opportunity for demonstrating that a carefully controlled convalescence can do much to secure a satisfactory leg. Typical bad and good results, respectively, are illustrated by the following two cases:

A 52-year-old unmarried woman, a cook, had noticed for three years slight intermittent pain and swelling of the lower left leg. Lameness had been aggravated for one month.

Examination revealed tight, full posterior calf muscles and tenderness over the superficial femoral vein above the knee. At operation, I had planned to interrupt the superficial femoral vein, but evidently (from the operative description) mistook the lower circumflex vein for the profunda, sectioning the common femoral. No thrombus was found. After a normal convalescence for several weeks, early return to work led to a recurrence of lameness and swelling. In spite of the use of an elastic stocking, postphlebitic induration and ulceration developed within two and one-half years.

The second case was that of a 37-year-old married woman, whom I had examined one year earlier because of incipient varicosity of the left saphenous vein. Some six months later, she became pregnant for the first time, and was subsequently subjected to a cesarean section. Nine days post partum, thrombosis was evident in the dilated saphenous vein of the left thigh and irritability of the calf muscles indicated an underlying deep thrombosis. At operation, a fresh soft clot was found to occupy the saphenous stump, but nothing could be sucked out of the common femoral. High division was made of the saphenous vein, with all entering branches, and ligation of the common femoral just proximal to the profunda. The immediate effect was alarming. Before the leg could be elevated on the operating table, it became blue and tense. The pulse rate rapidly increased and shock seemed imminent. However, on elevation of the legs to 30 degrees and saline venoclysis, the early signs of shock disappeared. The routine already outlined was then used. For the next three months the patient slept in a bed, elevated four inches at the foot, and undertook to see that the bandaged leg was given an opportunity to empty its veins by gravity whenever she had been obliged to do much standing in caring for her baby. I have never known anyone to behave so intelligently. As a result, four years later, after starting with an engorged, edematous leg, a blocked saphenous system, and ligated common femoral, she now uses no bandage or stocking, notices only a trifling swelling of the ankle after an especially long day on her feet, and has no postphlebitic sequelae. The patient is now again pregnant. At six months, there is no edema, no cyanosis, but an increase of varicosity in the saphenous system is noted.

From my experience of only four well-controlled observations upon unilateral common femoral vein interruption, I have received the impression that an immediate postoperative thrombotic reaction, marked by swelling and lameness in the calf, is more likely to follow common femoral vein interruption than any other procedure. As a late result, edema and venous congestion are not uncommon, especially in individuals who must do much standing or sitting without exercise. I have not been able to find studies comparing the end results of common with superficial femoral vein interruption. Donaldson,[6] in his survey of femoral vein interruption at the Massachusetts General Hospital (1937 to 1946), made no distinction between the two procedures. He stated, in effect, that any subsequent edema is directly proportional to the extent of the thrombosis at the time of operation. This, of course, must be true only in a very general way, and leaves out of consideration variations in the connections of the combined femoral systems with the veins above. I suggest that since Eger and Casper[7] have shown how very often no valve is present in the common femoral or external iliac vein, the profunda is quite capable of forwarding blood against gravity so long as the common femoral, even though freshly thrombosed, is not fully obstructed. It certainly cannot so act if the common femoral is ligated, especially since its connections with the circumflex veins are so few and small. And I find it hard to believe that the great saphenous, even though not itself

thrombosed or ligated, can carry much of the load. Indeed, my experiences of combined saphenous and femoral vein interruption have caused me to feel that the usefulness of the saphenous as a collateral has been exaggerated.

Of the four cases of common femoral vein interruption, one has an excellent result, one shows slight edema only, and the other two serious edema, postphlebitic induration, and ulceration. Discussion of the results in these few instances will be included in the general discussion.

Common Iliac Vein Interruption.—I[8] have reported before upon the use of this operation in cases of thrombotic disease in which a lower ligation has seemed likely to be ineffective in controlling embolism and especially when an advanced thrombosis has seemed to call for the best sort of collateral venous return. Investigation has shown that the end result has depended most accurately on the extent of the thrombosis at the time of the operation. I have reports covering five to eight years on six patients whom I am satisfied that the preoperative extent of the thrombosis was recognizable. In all, repeated pulmonary embolism was the occasion of the operation.

In four cases, the extent of thrombosis was believed to be slight, though repeated embolism had occurred. In these, the end result was excellent.

In one, both saphenous and superficial femoral veins were known to be involved. The end result was slight enlargement of the lower leg and ankle with edema only on long standing. There were no skin changes.

In another, thrombosis was advanced, and the leg blue to mid-thigh. Chronic swelling resulted in both these advanced cases, and in one of the two, postphlebitic induration and dermatitis.

Anticoagulant Therapy.—I have only ten patients accurately paralleling those treated by vein interruption, but their thromboses run all the way from the mild, early sort to advanced, high, femoral, nearly obstructive disease, attended by pulmonary embolism. The mild cases did well, under the usual graded convalescence, perhaps no better than patients treated by superficial femoral vein interruption, though it has seemed to me that the legs returned more rapidly to normal. But it is in the advanced disease, marked by high femoral vein involvement, that the good results of combined chemotherapy and physiotherapy seem especially to stand out. Three of the ten were of this sort, of which one was bilateral and persistent. One only will be described.

A 60-year-old man had been subjected to an appendectomy, and two days after going home, apparently well, had suffered a serious pulmonary embolism. On returning to the hospital, the right calf for the first time showed enlargement. Two days later I found the lower right leg considerably swollen with sufficient cyanosis to indicate a high femoral involvement. Operative surgery would probably have resulted in a bilateral common femoral interruption.

Although resistant to Dicumarol, the patient's prothrombin percentage was finally brought down to 20 and maintained at about that level for one week. Bandaging, elevation of the foot of the bed, and graduated exercises were employed. The patient was encouraged to continue gravity drainage and bandaging during the following year, at the end of which time only slight enlargement of the superficial veins below the knee without

edema remained. From the moment anticoagulation was employed, the state of the leg rapidly improved and there was none of the reaction so often seen in this sort of case after common femoral vein section.

Among the seven early cases, the end result in six is excellent. The seventh is an instance of recurrence after a bout of heparin with secondary treatment by Dicumarol. The immediate result was satisfactory, but the patient cannot be traced. Of the three advanced cases, one is described here as having an excellent result. The other two patients suffered from persistent high thromboses just short of obstructive thrombophlebitis. Both present, as a late result, slightly swollen limbs without cutaneous changes.

DISCUSSION

This report argues for treatment of venous thrombosis by anticoagulation with preservation of the common femoral pathway plus a carefully controlled scheme of physiotherapy. Blockage of the common femoral vein, that is, the outlet for both the deep femoral (profunda) vein and the superficial femoral, rather than disablement of the superficial femoral alone, would seem to represent what the Swedish school regards as a cause of permanent edema and its consequences. Superficial femoral vein section is a relatively harmless interruption, but since it offers insecure protection against embolism (once thrombosis has started), it must, if used, be supported by anticoagulation.

Those who include in the aftertreatment of their cases of thrombosis no other directions than early and persistent ambulation go only halfway. Certainly walking is better than standing or sitting, but one cannot walk always, and the newly used, and presumably delicate and dilatable collateral pathways, should not be overworked from the start. I recommend especially walking with the diminished hydrostatic venous pressure and weight-bearing shown among the exercises in Fig. 1.* A few minutes of this exercise can be carried out many times a day, alternating with bed rest. Dr. Warren has shown me his figures for the pressure-lowering effect of walking as compared with standing and sitting. He points out, what others, of course, have recorded, that the resting, erect venous pressure is the hydrostatic pressure of the column of venous blood from the point at which the needle is inserted in the vein to the level of the right auricle, plus about 10 cm. of strictly venous pressure. On walking, this pressure is lessened by almost 50 per cent. At the same time, lifting or straining tends to increase normal pressures both in the erect position and during exercise. Mere foot exercises in the sitting position cause no such a fall of pressure as actual walking. Bandaging the legs seems to me additional security against overdistention of the lower-limb veins. Indeed, the aim, I am sure, of both immediate treatment and convalescence, should be to keep venous pressures even and low. The collateral circulation which is thus developed under the influence of use should then remain permanently efficient.

*Dr. Richard Warren was kind enough to prepare this illustration for me at the Veterans Administration Hospital in West Roxbury.

SUMMARY

Experience with cases of early quiet thrombosis (phlebothrombosis) treated by vein interruption or by anticoagulation indicates that:

1. The consistent use of gravity drainage, graded exercises, bandaging, and the proper balance between dependency and elevation is of advantage in establishing a permanently efficient collateral venous return from the lower limbs, and is especially required after an extensive thrombosis.

2. The connections of the deep (profunda) with the superficial femoral vein are usually intimate and occasionally the two systems are practically one, but the combined systems have unsatisfactory collateral connections with higher veins.

3. The normal deep femoral system of veins may be expected to offer a good collateral pathway as long as the common femoral vein is open, whether or not the common femoral has been invaded by thrombosis.

4. Surgical obstruction of the common femoral vein necessarily and seriously opposes the establishment of an effective collateral circulation, but may be compensated for by especially prolonged physiotherapeutic measures during the immediate and remote convalescence.

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PHLEGMASIA CERULEA DOLENS AND GANGRENE ASSOCIATED WITH THROMBOPHLEBITIS

Case Reports and Review of the Literature

Michael DeBakey, M.D.,* and Alton Ochsner, M.D., New Orleans, La.

(*From the Departments of Surgery, Tulane University of Louisiana and the Ochsner Clinic*)

VASOSPASM in association with thrombophlebitis has been demonstrated both clinically and experimentally and is now generally recognized as a common accompaniment of that condition. However, the occurrence, in venous thrombosis of the extremities, of clinical manifestations of arterial involvement which are so severe as to simulate acute arterial occlusion, and which even terminate in gangrene, is extremely uncommon. A review of the recent medical literature reveals 56 cases of this type, in 24 of which gangrene developed. Only 3 reports[24, 41, 42] concerned particularly with this form of the disease appear in the American literature, most of the others having been recorded by French observers.

The extreme infrequency of this condition and the few reports on the subject in the American literature prompt the report of the following two cases, which represent the two different types of the disease. In addition, there are certain interesting features concerned with the pathogenesis of this unusual form of venous thrombosis which deserve further consideration.

REPORT OF CASES

Case 1.—A 22-year-old white man, who had had ulcerative colitis for twelve years, had been treated conservatively with good results until shortly before he was admitted to Touro Infirmary, Jan. 10, 1947. Surgical therapy was then decided upon because the clinical manifestations of diarrhea, tenesmus, and bloody stools could no longer be controlled by medical measures. At this time the patient's general condition was poor. He appeared chronically ill, dehydrated, and undernourished, and he had apparently lost considerable weight. Results of the physical examination were otherwise negative. The temperature ranged between 101 and 103° F. and the pulse between 100 and 120 beats a minute. The blood pressure was 112 systolic and 60 diastolic.

Results of laboratory investigations were negative, including fecal and bacteriologic examinations, except as follows. Blood: hemoglobin 43.5 per cent, 6.8 Gm. per cent; red blood cells, 2,500,000 per cubic millimeter; white blood cells, 8,300 per cubic millimeter; neutrophiles, 81 per cent; platelets, 620,000. The patient was reported to have severe secondary hypochromic anemia. Coagulation time was 1½ minutes, bleeding time 1 minute, and serum proteins 5.2 Gm. per cent.

On Jan. 27, 1947, the patient experienced a sudden, severe pain in the left leg in the region of Scarpa's triangle. It came on both abruptly and violently and was only partially relieved by morphine. Almost immediately after the onset of pain the limb became numb and cold and began to assume a bluish red color. Within one and one-half hours the normal coloration had been replaced by an intense, cyanotic, violaceous discoloration. Slight ecchymoses and areas of petechial hemorrhage were observed in the skin over the upper thigh, particularly in the region of Scarpa's triangle (Fig. 1). Within one-half hour after the onset of pain the extremity began to swell and within the next hour it became greatly

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*Now at the Department of Surgery, Baylor University, College of Medicine, Houston, Texas.

Fig. 1.

Fig. 3.

Fig. 1 (Case 1).—Photograph of lower extremities taken shortly after operation showing edema of left leg, particularly in thigh, with intense, cyanotic, violaceous discoloration of skin.

Fig. 3 (Case 2).—Photograph of lower extremities taken on Feb. 5, 1947, shortly after admission of patient to hospital, showing extensive swelling of both lower extremities with intense, cyanotic, violaceous discoloration of the skin. Purpuric areas, petechial-like lesions, and some blisters and bullae may be observed over the dorsum of the foot and leg on the left side and early gangrenous changes of the toes and distal portion of the foot are apparent on the right side.

swollen. Pulsations could be felt in the femoral artery and feeble pulsations could be felt in the posterior tibial and dorsalis pedis arteries when the patient was examined shortly after the onset; at the end of two hours, however, no arterial pulsations could be felt in the foot. Along with these changes in the limb, deterioration of the general condition occurred, which suggested circulatory collapse.

Pain was somewhat relieved by left lumbar sympathetic block with a 1 per cent solution of procaine hydrochloride, but the color of the leg did not change. Because of the manifestations of impending shock, the patient was given transfusions of whole blood and plasma.

Fig. 2 (Case 1).—Photograph of lower extremities taken approximately fifteen months after thrombotic episode showing left leg completely recovered.

Another physician, who saw the patient at this time (about one and one-half hours after the onset), made a diagnosis of phlebothrombosis of the pseudoembolic type and undertook surgical exploration of the femoral vein under spinal analgesia. A longitudinal incision was made beginning just above the inguinal crease and just medial to the femoral pulsation, and was extended downward for a distance of about 15 cm. There was considerable edema of all the tissues. After the superficial and deep fascia had been divided, the common femoral, superficial femoral, deep femoral (profunda), and saphenous veins were identified and freed. Coarse ligatures were placed loosely around these veins to provide a ready means for later hemostasis. The common femoral vein was greatly engorged but rather soft. The internal saphenous vein was also tense and full. The femoral artery was pulsating but was distinctly contracted. When the superficial femoral vein was opened, granular clotted blood (of the "currant jelly" type) began to ooze from it; when the incision was enlarged, still more clots escaped. A large clot was finally sucked out of the distal end of the vein and another from the proximal end. Removal of these clots was followed by free bleeding. The vein was ligated both above and below the incision and the wound was closed in layers.

Immediately following the operation there was definite improvement in the patient's condition. Pain was greatly relieved. The extremity began to feel warmer, discoloration was less intense, and pulsations in the foot returned. Improvement was gradual, but by the end of a week edema had completely subsided and by the end of two weeks discoloration had disappeared.

Ileostomy and appendectomy were performed, Feb. 25, 1947. Recovery was uneventful, and when the patient left the hospital on March 14, his general condition was much improved. The only significant finding in the extremities was a slight cyanotic tinge in the left foot and toes on dependency. An elastic bandage was advised.

When the patient was again examined, Nov. 3, 1947, approximately nine months after the thrombotic episode, his general condition had continued to improve. There was no edema of the left extremity and no functional disturbances were apparent. The only departure from normal was a slight discoloration of the toes on dependency, together with slight contraction of the toes.

The patient was last seen in May, 1948, when he returned for resection of the colon, which was followed by an uneventful convalescence. At this time, approximately fifteen months after the onset of the thrombosis, examination of the extremities revealed no abnormalities of any kind and it was evident that complete recovery had occurred (Fig. 2).

CASE 2.—A 40-year-old white woman was seen in consultation in a north Louisiana town on Feb. 2, 1947, for vascular disturbances involving both lower extremities. She had begun to suffer from vague generalized abdominal pain, chiefly on the right side, on Jan. 21, 1947, and had been hospitalized forty-eight hours later after melena had appeared. For the next three days both pain and melena increased in severity. The blood, which seemed to come from the large bowel, was dark and mixed with foul material. Results of physical examination at this time were negative except for some tenderness on the right side, particularly in the lower quadrant. Urinalysis, blood culture, fecal examination and culture, and roentgenograms of both the chest and the abdomen were essentially negative. The red blood cell count was 5,400,000 per cubic millimeter and the hemoglobin 80 per cent. The white blood count was 10,000 per cubic millimeter and the polymorphonuclear leucocyte percentage was 80.

On the fourth day of hospitalization after rectal bleeding had become less, a barium enema examination showed a definite, rather extensive filling defect in the cecal region and ascending colon just below the hepatic flexure; whether it was of malignant or of inflammatory origin could not be determined. For the next day or two pain and tenderness were more definitely localized in the right lower quadrant and it was thought that a mass was developing in this area.

On January 28, the eighth day of illness, edema was observed in the right lower extremity; within forty-eight hours the edema became massive in extent, involving the whole extremity and presenting the appearance of phlegmasia alba dolens. The following day a similar condition developed on the left side. On the same day a deep violaceous discoloration with purpuric areas appeared over the toes and dorsum of the right foot.

Although lumbar sympathetic blocks were carried out on January 30 and 31, the areas of discoloration became larger and deeper, coalesced, and eventually presented a typical picture of early gangrene.

The administration of penicillin was begun as soon as the patient was admitted to the hospital but was discontinued at the end of seventy-two hours because of the appearance of a skin rash. The only other active therapy consisted of several transfusions of plasma and whole blood.

When the patient was first seen in consultation on Feb. 2, 1947, she appeared somewhat drowsy but perfectly rational and complained only of moderate discomfort in both lower extremities. The temperature at this time ranged between 100 and 101° F. and the pulse rate was 100 to 110 per minute. Positive findings were limited to the abdomen and

lower extremities. Definite tenderness was elicited on the right side, especially in the right lower quadrant, and there was some rigidity in this area. An indeterminate mass was also palpable.

Both lower extremities were extensively swollen, the left more than the right. On the left side the swelling was diffuse and pitting and involved the entire extremity. The edema was suggestive of phlegmasia alba dolens, but the superficial veins were not as prominent as they usually are in that condition. The skin was pale and the temperature seemed slightly lower than normal. Pulsations in the dorsalis pedis, posterior tibial, and femoral arteries were not palpable but might have been obscured by swelling. Sensation was normal. There was considerable tenderness in the calf and on the medial aspect of the thigh.

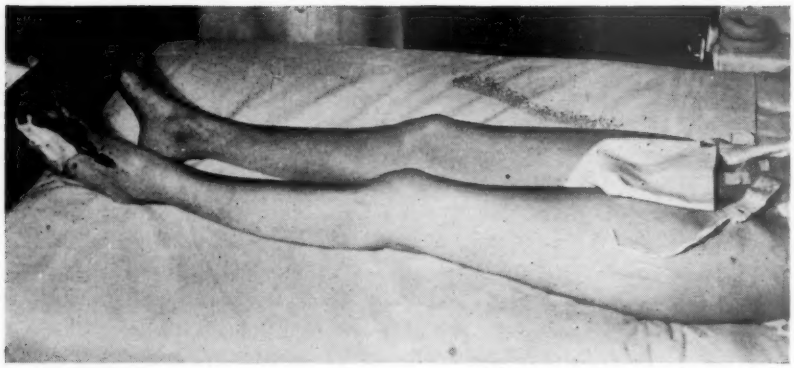
On the right side swelling in the thigh had apparently subsided somewhat, although the leg was still tensely swollen to the knee. A distinctive blackish discoloration, suggestive of early dry gangrene, was present over the toes and dorsum of the foot; it was more extensive on the outer than on the inner aspect. This discoloration, as it extended upward to just below the knee, gradually merged into a purplish, deep red, and then into a brighter red discoloration. Some large blebs or bullae were present over the dorsum of the foot and just above the ankle, where swelling was particularly tense. Pulsations of the femoral artery were palpable, but the dorsalis pedis and posterior tibial arteries could not be felt. Sensation was normal to the mid-dorsum of the foot, then it gradually diminished and finally disappeared entirely in the apparently gangrenous area. Tenderness on the right side was limited to the calf. Motion, although present, was much diminished.

After the initial examination, the abdominal lesion, because of the manifestations of peritoneal irritation and the multiple locations in the cecum and ascending colon, was thought to be inflammatory rather than malignant, though malignancy naturally could not be excluded until the abdomen was opened. This lesion, it was thought, had precipitated a severe thrombophlebitis, probably of the iliofemoral region, with later extension to the iliac vein on the right, and still later involvement of these vessels on the left. It was further postulated that severe arteriospasm had affected the lower leg and foot and that this factor superimposed upon the massive thrombosis had resulted in arterial thrombosis in the lower vascular channels and accounted for the development of gangrene in these areas. The concept of arteriospasm was supported by the fact that on the left side the extremity was pale and colder than normal and seemed to show rather poor filling of the superficial veins. On the right side, vasospasm and thrombosis seemed a more reasonable explanation of the pathologic condition than arterial embolism because pulsations were present in the femoral artery and the circulation in the thigh seemed normal.

Anticoagulants were not regarded as indicated because of the presence of an active bleeding lesion. The therapy advised consisted of transfusions, the red blood cell count now being 3,000,000 per cubic millimeter and the hemoglobin 60 per cent; continued daily lumbar sympathetic blocks; maintenance of the lower extremities in a position at, or slightly below, heart level; protection of the extremities from the weight of the bed covering and other trauma; and the use of all possible measures to prevent infection. It was thought that amputation of the right leg would eventually be necessary after demarcation had occurred. It was also thought that abdominal exploration would be necessary to determine the character of the cecal lesion and its appropriate treatment.

On February 3, the day after the examination recorded, discoloration similar to that present on the right side appeared in the left foot, and on the following day the patient was removed to New Orleans by ambulance. On the way to the city she experienced, for the first time, a sharp pain in the right chest. Examination on arrival was substantially the same as when she had been seen forty-eight hours earlier except for the discoloration in the left foot and leg and the fact that edema of the lower extremities now extended symmetrically to the level of the umbilicus, where it was rather sharply demarcated from normal tissues (Fig. 3).

All the laboratory examinations originally performed were repeated, with the same negative findings. The red blood cell count was now 3,750,000 and the white count 24,550 per cubic millimeter. The hemoglobin was 10.1 Gm. per cent, the hematocrit 35, and the



A.

B.

C.

Fig. 4 (Case 2).—Photographs of lower extremities of patient taken April 21, 1947, approximately three months after onset of condition. (*A*) The edema has completely subsided, the cutaneous discoloration has disappeared, and (*B* and *C*) the gangrenous areas in the toes and feet are well demarcated.

neutrophilic percentage 83. Sternal marrow studies revealed no significant findings. The platelet count was 93,750 per cubic millimeter; the bleeding time was 1 minute and coagulation time 3 minutes, 15 seconds. The prothrombin time was 70 per cent of normal. Results of agglutination tests, blood chemical determinations, blood culture, and sputum examination were negative. Serum proteins were 5.75 Gm. per cent (albumin 3.16 and globulin 2.59). Roentgenograms of the chest showed increased density in the right lower base, and subsequent serial studies pointed more and more to the diagnosis of pulmonary infarction.

The patient gradually improved under a regimen of penicillin, transfusions, and the usual supportive measures. The temperature, which had been about 100° F., gradually fell and reached normal on Feb. 22, 1947. Abdominal pain and tenderness disappeared and the mass in the lower right side became only questionably palpable.

Edema of the abdomen and lower extremities slowly disappeared, the areas of gangrene began to demarcate, and on February 13 the pulsations in the dorsalis pedis and posterior tibial vessels on both sides became palpable. Gynecologic examination on March 3 showed no abnormalities.

Fig. 5 (Case 2).—Photograph of lower extremities of patient taken on May 21, 1948, approximately sixteen months after onset of condition, showing final result of reparative procedures on feet. The patient is able to walk with a good gait using specially made shoes.

Barium enema examination on March 12 showed the cecum contracted to a narrow tubular channel, with the constricted segment sharply demarcated from the apparently normal bowel. A tentative diagnosis of ameboma was made, despite the fact that results of proctoscopic examination and purgative stool studies were negative, and emetine was given for ten days. At the end of this time another barium enema examination showed the same observations as well as a fairly well-visualized appendix. The diagnosis of appendicitis had not previously been entertained because of a history of appendectomy for acute appendicitis and the presence of a McBurney scar in the right lower quadrant.

The abdomen was explored on March 21, under spinal analgesia, through a low paramedian incision. The cecum was bound down by relatively recent adhesions, in which the appendix was included and from which it was freed with some difficulty. It was retrocecal and perforated at the base. At the site of perforation was a small, well walled-off abscess. The appendix was removed and the defect in the cecum at the appendicocecal junction was repaired. A small follicular cyst was removed from the right ovary. Exploration of the pelvic area showed a normal arterial tree. The iliac veins, however, were completely thrombosed on both sides and were represented only by fibrous cords up to their junction with the vena cava and as far distally as palpation was possible. The specimen excised for examination from the vein on the right was completely filled with a well-organized thrombus, which on histologic examination showed some recanalization.

The postoperative course was satisfactory except for the development of a localized pericecal abscess, which required drainage. The gangrenous areas on the lower extremities were permitted to become fully demarcated (Fig. 4) and on April 25 the large toe and the

second toe on the left foot and all the toes and part of the dorsum of the right foot were amputated. It was believed that the patient would have a functioning extremity on this side as well as on the left. Beginning May 3, 1947, and in successive stages ending June 27, the defects on both feet were satisfactorily covered with skin grafts. The patient was discharged from the hospital on Aug. 16, 1947, on a regimen of gradually increasing exercises.

The patient returned for observation on Nov. 24, 1947. Her condition was found to be satisfactory. She had gradually begun to bear weight partially on the left foot, with the aid of crutches and the use of specially made shoes. She had also continued to wear elastic bandages on both lower extremities. No edema had occurred.

The patient was again observed March 22, 1948. At this time it was noted that sensation had advanced over the entire plantar surface of the flap on the right foot. Full weight-bearing on both feet was begun after a special shoe was made for the right foot.

When she was last observed on May 21, 1948, the patient was able to walk unaided with a good gait. She had continued to wear elastic bandages and there was no edema of the extremities. Only slight color changes were observed on dependency (Fig. 5).

CLINICAL PICTURE

The first of these cases is characteristic of the condition known as pseudo-embolic phlebitis, the so-called blue phlebitis,[21] or phlegmasia cerulea dolens. Since 1929, when Tremolieres and Veran first directed attention to it, approximately 32 cases have been recorded in the literature.[46] The condition is undoubtedly more frequent than these reports would suggest, but it is still, according to our experience, an unusual form of venous thrombosis.

Most of the reported cases, like our own, follow a fairly consistent pattern. The clinical manifestations, all of which come on suddenly and progress rapidly, consist chiefly of pain, edema, discolorations, and vascular impairment.

The pain, which usually comes on with the greatest suddenness, is excruciating and is often difficult to control with anodynes. It is located first in the calf or groin but eventually involves the whole limb.

Almost as striking as the violence of the pain is the discoloration of the limb which takes place immediately after the onset, sometimes within a matter of minutes. The color is deeply violaceous or cyanotic, and often purpuric areas of petechial-like lesions are scattered over the extremity. Sometimes this discoloration assumes a mottled or marbled appearance. The discoloration usually begins in the lower portion of the limb and extends upward, but it may be more intense in the region of the thigh, particularly in and near the femoral area.

Swelling of the extremity usually takes place rapidly, though in some instances it develops slowly. As the swelling becomes more intense, cutaneous blebs and even bullae may appear. The cutaneous temperature of the involved extremity is likely to be diminished in comparison with the temperature of the normal side, and during the early phase of the episode there is almost invariably diminution in cutaneous sensation as well as in motility.

Shortly after the onset, pulsations in the arteries of the extremity become diminished and may disappear entirely. This observation, together with the temperature changes, alterations in cutaneous sensation, and loss of motility, is strongly suggestive of arterial involvement and has led to exploration on the mistaken diagnosis of acute arterial occlusion or embolism.[2, 23, 30, 36, 40, 45]

Clinical manifestations of circulatory collapse often accompany or immediately follow the onset of the condition and are likely to be impressive. They include pale facies, weak pulse, tachycardia, and sometimes a lowering of the blood pressure. The patient is extremely anxious and has a sensation of impending death. These manifestations are probably related to the extent of the thrombosis, edema, and loss of fluids in the involved extremity. In the most severe cases the patient does die, never recovering from the initial state of circulatory collapse.

Most of the reported cases of blue phlebitis have occurred in the adult age group, from the third to the fifth decades, with both sexes affected about equally. The condition may involve any extremity but it has been observed most frequently in the left lower extremity. Among the 26 reported cases in which this information was recorded, 2 were in the upper (one on the right side and one on the left), and 24 were in the lower extremities, of which 7 were on the right side and 17 on the left. No particular circumstance seems to predispose to its development though some type of infection, including medical and surgical infections and puerperal sepsis, is often present. In an occasional case the condition has appeared after a relatively minor injury or in an apparently healthy individual. Of interest in this connection is the report of Bargen and Barker,[7] who observed 5 cases of venous thrombosis in patients with ulcerative colitis, in 3 of which the manifestations closely resembled the form of blue phlebitis under discussion. It is noteworthy that although Bargen and Barker commented upon the frequency of venous thrombosis in ulcerative colitis, among the recorded cases of blue phlebitis those reported by these observers are the only ones, aside from our first case, with a background of ulcerative colitis.

The gravity of this form of venous thrombosis is shown by the fact that death occurred in 8 of the 32 cases recorded. In most of these cases death occurred shortly after the onset of the condition, the patient never recovering from the initial state of circulatory collapse. It is interesting that although 6 patients in the entire group showed manifestations of pulmonary infarction, only 1 of the 6 died.

The subsequent course of patients who recover from the initial episode is fairly characteristic of phlegmasia alba dolens or the more common form of iliofemoral thrombophlebitis with gradual disappearance of cutaneous discoloration, progressive subsidence of edema, and return of normal arterial pulsations. In many of the recorded cases ultimate recovery was complete and there were few or no residual postphlebitic manifestations.

The second case which we are reporting represents an even more severe type of venous thrombosis, in which actual gangrene of a part of the extremity occurs. One of the earliest instances of this kind was reported in 1932, by Bergeret, Guillaume, and Delarue.[8] To date, about 24 cases have been reported in the literature,[47] the most recent by Haimovici and Suffness,[24] in 1948. The age and sex distribution is similar to that observed in blue phlebitis. No preceding or associated illness seems characteristic, but most of the patients had

had some type of infection, such as appendicitis, peritonitis, puerperal sepsis, or pneumonia. One or two had suffered some injury of the extremity, and one had a malignant disease.

Whereas the onset and clinical manifestations in this group of cases may be similar to those of blue phlebitis, in a few of the recorded cases, as in our own, the onset was less dramatic and pain was less severe. In Gregoire's case the patient had only a moderate degree of pain in the foot, and in the case reported by Bergeret, Guillaume, and Delarue the clinical picture developed rather gradually. In other words, the early course of the disease may take one of two possible forms. In the first, it may suggest a typical thrombophlebitis or phlegmasia alba dolens, with the subsequent development of fairly characteristic arterial manifestations. In the other, the sequence of events is reversed; characteristic arterial manifestations appear at the onset and the subsequent course of the disease may suggest phlegmasia alba dolens.

In all cases, regardless of the character of the onset, the violaceous discoloration of the affected limb becomes more intense until typical gangrene gradually appears, usually in the toes and the distal portion of the foot. In some instances, the gangrenous process may spread up the leg; in others it becomes well demarcated. Any extremity may be involved but it seems to occur most frequently in the left lower extremity. Occasionally bilateral involvement has been observed, as in our case.

The prognosis in cases of venous thrombosis associated with gangrene is not good. Death occurred in 11 of the 24 recorded cases, and in all but 3 of the remainder a major amputation of the extremity was necessary. In those 3 cases, as in our own, only a portion of the foot and toes was lost.

Pulmonary infarction occurred in 2 of the 24 recorded cases, as it did in our second case, and in an occasional instance was the first manifestation of the venous thrombosis.

THERAPY

Numerous therapeutic measures, none of them strikingly successful, have been employed in this form of venous thrombosis. Attempts to produce vasodilatation and counteract vasospasm have included the use of vasodilator drugs such as acetylcholine and papaverine and procaine hydrochloride block of the regional sympathetics or periarterial sympathectomy. In some cases dramatic improvement occurred but it was usually temporary, except in a few instances in which recovery occurred without gangrene. Similar recoveries, however, have followed the use of other conservative measures.

Operative intervention, consisting of exposure of the femoral vessels, thrombectomy, and periarterial sympathectomy, has not been notably successful. On the other hand, the striking results which followed thrombectomy and ligation in the first of the cases reported in this communication would seem to warrant this type of therapy. It would also seem indicated as a prophylactic measure, to guard against pulmonary infarction and embolism, which are not infrequent accompaniments of this condition. Lumbar sympathetic block with procaine to counteract vasospasm also seems indicated.

If gangrene has occurred, every effort should be made to control infection and permit the process to become demarcated. In the majority of instances the gangrene is of the dry type and the eventual loss of tissue is usually not as great as at first seems likely to occur. For this reason, a conservative attitude should be taken toward amputation, which should be postponed until the full extent of the eventual tissue loss has become apparent.

PATHOGENESIS

The form of venous thrombosis discussed in this communication is distinctly different from the ordinary varieties of phlebothrombosis and thrombophlebitis. The dramatic, often violent onset, the striking clinical picture, and the severity of the manifestations bear little resemblance to the clinical manifestations of the other forms. Particularly impressive are the manifestations which apparently reflect involvement of the arterial tree. They are characteristic and are often so pronounced that, as has already been mentioned, they suggest the diagnosis of acute arterial occlusion and in some instances have actually led observers into surgical exploration of the arteries for the presumed occulsive process.

These various considerations naturally raise certain questions as to the pathogenesis of this type of venous thrombosis and as to the reasons for the difference between it and the more common milder forms. Since, however, the etiology of the more common types is still poorly understood, it is natural that no satisfactory explanation for the more infrequent and more severe form can be advanced. The violence of the onset, as Magendie and Tingaud[32] noted, and the severity of the manifestations suggest that the phenomenon of intravenous coagulations occurs suddenly, with the "brutality of a physicochemical reaction." But what are the factors that precipitate such a reaction? And why are these factors, whatever they may be, operative in some cases and not in others? It is well known that in phlebothrombosis an extensive thrombotic process may be present when there are few local or systemic clinical manifestations, or none at all. Even in phlegmasia alba dolens, the classical form of thrombophlebitis, thrombosis may be extensive whereas clinical manifestations develop only gradually. Why do these forms of thrombosis assume a less violent or actually mild character? Obviously in the severe form we are discussing some changes occur in the coagulative mechanism which lead to sudden and massive thrombosis. The nature and cause of the process, however, remain to be clarified.

Of particular interest in the pathogenesis of the severe form of venous thrombosis are the arterial manifestations and the occurrence of gangrene, particularly its occurrence in the absence of organic lesions of the arterial tree. The absence of such lesions has been clearly demonstrated in many of the reported cases by careful studies, including arteriography, complete dissection of amputated extremities, autopsy observations, and extensive histologic examinations of the vessels. These studies have confirmed the absence of organic arterial lesions and have shown that thrombosis of the venous system is so extensive as to include even the smallest radicles.

Two factors, spasm and massive venous obstruction, have been postulated as responsible for the striking arterial manifestations in the severe types of venous thrombosis. The role of vasospasm in their productions is difficult to evaluate. Some observers are inclined to regard it as important. Others doubt that it plays a significant part, or indeed any part at all. There is strong evidence of arterial spasm in many of the reported cases. Its presence is suggested clinically by the diminution or absence of arterial pulsations and oscillations in the early state of the condition, while their subsequent return to normal is associated with improvement in the condition of the limb. Other evidence of the presence of vasospasm lies in the contracted appearance of the artery at operation and the dramatic, though often temporary, improvement in pulsations following sympathetic block or the administration of vasodilating agents. It has been demonstrated clinically and experimentally that vasospasm exists in thrombophlebitis and that this vasospastic action can be abolished by the interruption of the regional sympathetic pathways.[12, 35] It has also been shown that this vasospasm in acute phlebitis involves the veins as well as the arteries and that it is probably responsible in great measure for the pain.[38] The fact, however, that the severe type of venous thrombosis may continue to progress to actual gangrene in spite of vigorous antivasospastic measures and the transient improvement produced by them seems to indicate that vasospasm does not play a primary role in the genesis of this condition. It would seem, in fact, that in the mechanism of its production some factor or factors other than vasospasm play the dominant role and that the role of vasospasm is merely temporary and contributory to the ischemic process.

The second, and more plausible, explanation of the mechanism involved in the ischemic disturbance is blockage of the circulation by venous thrombosis. What this amounts to is that although blood can enter the extremity through the patent arterial tree, it cannot leave it because the venous circulation is obstructed by thrombosis. This interference with the circulation soon leads to stasis of the arterial blood flow, at least in the more terminal parts of the vascular bed, with resulting ischemia, anoxia of the tissues, and gangrene.

That such a mechanism is possible has been demonstrated experimentally. Fontaine and Pereira[18] have shown that gangrene could be produced in animals only when there was complete blockage of the venous blood flow. We[9] have also shown experimentally that a profound effect upon the peripheral pulse volume occurs when a significant increase in the venous pressure is produced by obstruction of the main venous outlet of an extremity. Following occlusion of the venous channel in these experiments, the rise in venous pressure was 13.9 times the normal value, whereas the simultaneous decrease in volume of pulsations was 51.5 per cent. It was possible to show that the great reduction in the volume of pulsations was probably caused by the reduction in the elastic properties of the vessels caused, in turn, by mechanical distention.

It is thus apparent that obstruction of the venous return in an extremity, provided that it is of sufficient extent, can cause a great reduction in the arterial blood flow. On this basis it seems reasonable to assume that in cases of severe

venous thrombosis associated with gangrene the primary factor responsible for the arterial manifestations is massive venous occlusion. Blockage of the venous return, however, in addition to being practically complete, must take place suddenly to produce the results described. This may conceivably initiate an immediate and severe degree of vasospasm which, as emphasized by some observers,[2-5, 21, 25, 31, 32, 37, 43-45] would tend to aggravate the ischemic process. These conditions, as Fontaine, Israel, and Pereira[17] have pointed out, are only occasionally met, because of the richness and abundance of the collateral venous channels. Fortunately, therefore, the clinical condition is likely to be encountered only very infrequently.

SUMMARY

1. The occurrence, in venous thrombosis of the extremities, of clinical manifestations of arterial involvement which are so severe as to simulate acute arterial occlusion, and which even terminate in gangrene, is extremely uncommon. A review of the recent medical literature reveals only 56 cases of this condition.

2. Two cases, representing the two different types of venous thrombosis (pseudoembolic phlebitis and venous thrombosis with actual gangrene of the extremity), are reported.

3. The clinical manifestations follow a consistent pattern. In both forms of the disease the condition is associated with rather striking clinical manifestations which develop suddenly and progress rapidly, consisting chiefly of severe pain, edema, cyanotic violaceous discoloration, and evidence of arterial deficiency. The early course of the second form, in which gangrene occurs, may suggest a typical thrombophlebitis or phlegmasia alba dolens, with the subsequent development of fairly characteristic arterial manifestations, or the sequence of events may be reversed.

4. Both conservative measures, such as the use of vasodilator drugs and procaine hydrochloride block of the regional sympathetics or periarterial sympathectomy, and operative intervention, consisting of exposure of the femoral vessels, thrombectomy, and periarterial sympathectomy, have been advocated. None has been strikingly successful.

5. The prognosis in both forms of the disease is grave.

6. Evidence is offered which suggests that sudden complete blockage of the circulation by venous thrombosis is the primary factor in the mechanism involved in this ischemic disturbance. Vasospasm is believed to play a secondary and contributory role in the pathogenesis of this condition.

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THE EARLY RESULTS OF SYMPATHECTOMY IN FAR-ADVANCED ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

FREDERICK A. COLLER, M.D., KENNETH N. CAMPBELL, M.D., BRADLEY M. HARRIS, M.D., AND ROBERT E. L. BERRY, M.D., ANN ARBOR, MICH.

(From the Department of Surgery, University of Michigan Medical School)

INDIVIDUALS suffering from the effects of obliterative arteriosclerosis of the peripheral vessels have long been thought to be beyond the reach of surgical aid by measures destined to improve the circulation. This conclusion is not compatible with our experiences or with the observations of other investigators who have performed lumbar sympathectomy on these patients. The belief that interruption of the autonomic nervous system pathways has little to offer these patients is not tenable if one reviews the numerous reports from vascular clinics of satisfactory results following sympathectomy for arteriosclerosis obliterans.[1-9]

Subsequent to the report of White[10] on the technique of blocking the lumbar sympathetics with procaine hydrochloride, Flothow,[12, 13] Reichert,[14] and Baker[15] observed that blockade, by chemical means, of the lumbar sympathetic chain in peripheral arteriosclerotic vascular disease often produced unanticipated good results. Permanent interruption of the lumbar sympathetic chain by ganglionectomy has been performed by several investigators for obliterative sclerosis of the peripheral arteries. Ives[6] performed sympathectomy on seven patients in whom the outstanding symptom was intermittent claudication. The average age of his group was 60 years. Six of the results he classed as favorable. One patient obtained no relief. Harris[5] has reported thirteen lumbar sympathectomies in patients with advanced peripheral arteriosclerosis, with 40 per cent good results. Atlas[1, 2] followed twelve cases for a period of at least twelve months; seven patients obtained relief from intermittent claudication, three were classified as improved, while two were unimproved. He observed further that walking capacity was rarely immediately increased; many months often were necessary for maximum benefit. Trimble, Cheney, and Moses[7] observed benefits obtained in twenty-four sympathectomized individuals, all having been followed for more than twelve months. Eight of these were classified as greatly improved, nine showed some improvement, and four obtained no relief. Freeman and Montgomery[4] reported six lumbar sympathectomies performed on individuals with intermittent claudication. They observed an increase in walking distance from one to fifteen blocks following this procedure. De Takats and co-workers[3] reported twenty-five sympathectomies on individuals with peripheral arteriosclerosis. They divided their cases into four groups based upon the degree of claudication and severity of trophic changes. All of their cases were benefited to some degree by operation. They further

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concluded that: (1) Extremities warm faster and cool slower on direct exposure after sympathectomy; (2) the high vasoconstrictor tonus in the sitting or standing position is abolished; (3) vascular exercises are more effective; and (4) cross stimulation between sympathetic and demyelinated sensory fibers is abolished. Yeager and Cowley[8] published the resultant effects of lumbar sympathectomy in 150 cases. Of this group they classified forty-six (30.66 per cent) as improved. In fifty-six patients amputations were necessary following sympathectomy. They observed, however, that seventy-three patients in this series did not have adequate preoperative vascular studies. The recent report of Freeman, Leads, and Gardner[9] gave an excellent summary of the entire subject.

In 1945 we became interested in the possibilities of salvage, by lumbar sympathectomy, of extremities affected by far-advanced arteriosclerotic peripheral vascular disease with associated ulceration and gangrene. This group had previously been doomed to ultimate amputation in a very high per cent of cases because of the advanced stage of their disease. It was felt that if any significant percentage of them could be rehabilitated, following sympathectomy, an important advance in the therapy of this heretofore rather hopeless group would have been achieved.

During the two and one-half year period from July 1, 1945, to Jan. 1, 1948, there were 350 patients with arteriosclerotic peripheral vascular disease seen in the surgical outpatient department. Two hundred twenty of these were classed as Grade III or IV according to the classification proposed by de Takats and co-workers.[3] During this same period, 103 lumbar sympathectomies have been performed in 83 patients who had not previously been considered satisfactory candidates for this operation.

Certain patients, however, were not considered suitable subjects for sympathectomy because of far-advanced cerebral and renal arteriosclerotic involvement. Furthermore, it was felt that the operation was not indicated in patients with cardiac decompensation that could not be adequately controlled. Poor results were observed early in the series in patients with paradoxical response to paravertebral block, that is, those whose symptoms were aggravated or showed evidence of deleterious effect upon the remaining circulation, and in patients presenting marked atrophy of the soft tissues with resultant skeletization. These patients were subsequently excluded from operative consideration.

Individuals selected for lumbar sympathectomy were considered suitable if they demonstrated (1) some response to sympathetic block, either subjective symptomatic relief or temperature rise in the involved extremity; (2) evidence of arrest or improvement of the process on a period of conservative therapy which included:

(a) complete cessation of smoking
(b) control of diabetes when present
(c) periodic autonomic block with tetraethylammonium chloride[11] or paravertebral lumbar block

(d) Buerger-Allen exercises
(e) chemotherapy directed at control of whatever infection was present.

(3) as a last resort in patients showing lack of response to conservative measures and in whom no specific contraindication existed.

The operative approach utilized was a transverse flank incision with extraperitoneal dissection. Patients were made ambulatory the same afternoon or the day following operation and were discharged when the skin sutures were removed, usually about the seventh day. Spinal anesthesia was preferred. Those patients presenting a moderately severe hypertension were given gas-oxygen-ether inhalation anesthesia.

This report will concern itself with the first 63 patients operated upon prior to July 1, 1947, inasmuch as these have been followed a sufficient period of time to allow a more critical evaluation.

Of this group, 50 were men and 13 were women, a ratio of 4:1 of men over women. The youngest patient was 32 years of age, the arteriosclerotic process having been proved by pathologic examination. The oldest patient was 75 years. By far the greatest number of patients were in the sixth and seventh decades (51 to 70 years). Average age of this group was 58.2 years (Table I).

TABLE I. GENERAL STATUS ON ADMISSION OF PATIENTS WITH FAR-ADVANCED ARTERIOSCLEROSIS OBLITERANS WHO UNDERWENT LUMBAR SYMPATHECTOMY

Number of patients			63
Sex of patients			
Males	50		
Females	13		
Ratio	4:1		
Age (years)			
31 to 40		1	
41 to 50		7	
51 to 60		32	
61 to 70		18	
71 to 80		5	
Youngest patient		32	
Oldest patient		75	
Average age		58.2	
Extremity involvement			
Left lumbar sympathectomy		27	
Right lumbar sympathectomy		25	
Bilateral sympathectomy		11	
One stage	9		
Two stage	2		
Duration of symptoms			
Less than 1 month		6	
1 to 6 months		15	
6 to 12 months		10	
1 to 2 years		10	
2 to 5 years		13	
5 to 10 years		9	

Seventy-four lumbar sympathectomies were done on the 63 patients. Of 11 bilateral operations, 9 were done in one stage and 2 in two stages. A left lumbar sympathectomy was done in 27 patients and a right in 25, the incidence of involvement of the lower extremities being about equal.

TABLE II. PRESENTING SYMPTOMS OF SIXTY-THREE PATIENTS UNDERGOING LUMBAR SYMPATHECTOMY

SYMPTOMS	NUMBER	PER CENT
Pain in the extremity	59	93.6
Symptomatic cold feet	45	71.4
Intermittent claudication	31	49.2
Ulceration	40	63.5
Gangrene	40	63.5

Symptoms causing these patients to seek medical aid varied greatly in composition and number (Table II). Pain in the extremity was present in 59 cases (93.6 per cent); symptomatic cold feet, 45 (71.4 per cent); intermittent claudication, 31 (49.2 per cent); ulceration, 40 (63.5 per cent); and gangrene, 40 (63.5 per cent).

Duration of symptoms prior to being seen at the University Hospital are shown in Table I. Less than 50 per cent had the symptoms for shorter periods than one year. Nine patients (14.3 per cent) had the onset of symptoms more than five years prior to their first visit at the hospital.

Twenty-one (33.3 per cent) patients had diabetes mellitus. Only 4 were considered adequately controlled at the time of admission. The remaining 17 were uncontrolled, poorly controlled, or undiagnosed when first seen. Results of sympathectomy in this group will be presented in detail later.

Some atrophy of the involved extremity was observed in 38 patients (60.3 per cent). The posterior tibial and dorsalis pedis pulses were absent in 53 cases. The femoral pulse was absent in only 3 patients. Nine cases presented a single palpable pedal pulse or questionably palpable pulses. No record of pulses was obtainable in one case. Infection sufficiently severe to necessitate administration of antibiotics was observed in 13 patients.

Final grading[3] of these patients was as follows: Grade I, 0; Grade II, 4; Grade III, 12; Grade IV, 47.

TABLE III. RESPONSE OF PRESENTING SIGNS AND SYMPTOMS FOLLOWING LUMBAR SYMPATHECTOMY

SYMPTOMS	NUMBER	RELIEF, ARREST, OR IMPROVEMENT	PER CENT
Pain in the extremity	59	46	78.2
Symptomatic cold feet	45	32	71.1
Intermittent claudication	31	27	87.0
Ulceration	40	23	57.5
Gangrene	40	28	70.8

RESULTS OF OPERATION (TABLE III)

Pain (Table IV).—Fifty-nine patients complained of pain in the involved leg varying from minimal distress to constant disabling rest pain. Of these,

TABLE IV. RESPONSE TO LUMBAR SYMPATHECTOMY OF PATIENTS WITH PAIN IN THE EXTREMITY DUE TO ARTERIAL INSUFFICIENCY

Patients with painful extremities	59
Constant rest pain	31
Total relief of pain	28
Partial relief of pain	18
No alleviation or subsequent amputation	13

28 (47.5 per cent) were completely relieved of pain following sympathectomy. Another 18 (30 per cent) patients obtained some alleviation of pain. The remainder obtained no help and all but 2 of these finally had amputations.

Cold Feet (Table V).—Of the 45 patients complaining of cold feet, symptomatic relief was obtained in 32 cases (71.1 per cent). Two obtained no help, and the remainder without relief eventually had amputations.

TABLE V. RESPONSE TO LUMBAR SYMPATHECTOMY OF SYMPTOMATIC COLD FEET

Number of patients	45
Symptomatic relief	32
Persistence of symptoms	2
Subsequent amputation	11

Intermittent Claudication (Table VI).—Of 31 cases with intermittent claudication, 27 (87.0 per cent) patients obtained some measure of improvement or arresting of symptoms. Six out of 7 with unilateral moderately severe claudication obtained relief. Of the group of 10 with unilateral severe claudication, 9 were helped. The results were just as good with bilateral intermittent claudication. Both patients with moderately severe involvement obtained relief, while 10 out of 12 with severe involvement obtained significant alleviation. The 4 patients who obtained no benefit eventually had amputations. It must be clearly understood that although some benefit was obtained in 87 per cent that no patient obtained unlimited walking distance from operation.

TABLE VI. RESULTS OF SYMPATHECTOMY IN PATIENTS WITH INTERMITTENT CLAUDICATION

INTERMITTENT CLAUDICATION	CASES	IMPROVED OR ARRESTED	PER CENT
Unilateral moderately severe	7	6	85.7
Unilateral severe	10	9	90.0
Bilateral moderately severe	2	2	100.0
Bilateral severe	12	10	83.3
Resultant effect in all cases not responding to sympathectomy was amputation			
Totals	31	27	87.0

Ulceration (Table VII).—Forty patients presented ulcerations secondary to arteriosclerotic ischemia. There were multiple ulcerations in 7 cases, the largest number in any one case being 11. Thirty-three in this group also had

TABLE VII. RESPONSE TO LUMBAR SYMPATHECTOMY OF PATIENTS WITH ARTERIOSCLEROTIC ULCERATION

Patients with arteriosclerotic ulceration			40
Total sites involved		50	
Toes	27		
Malleolus	7		
Foot	13		
Leg	2		
Previous amputation site	1		
Multiple ulcerations	7		
Largest number single case	11		
Associated gangrene	33		
Rapid healing following sympathectomy			14
Improvement with delayed healing			9
Failure to heal ulcerations or subsequent amputation			17
Percentage evidencing healing or rapid improvement			57.5%

associated gangrene. Following sympathectomy 14 patients had rapid healing of the ulcerations. Nine others were improved but the healing was delayed. Results in these 23 patients were considered satisfactory and constituted 57.5 per cent of the group. The remaining patients received little if any benefits from operation. Many of these fell into the group that eventually had amputations. It is of interest to note that one patient who underwent lumbar sympathectomy in this group returned to the hospital one year later with far-advanced arteriosclerotic involvement of the opposite leg that necessitated amputation. The sympathectomized limb had healed promptly after operation and was in good condition at the time of readmission.

Gangrene (Table VIII).—Gangrenous involvement in sympathectomized patients, for the most part, was localized to the toes. In only 5 cases was the foot involved. Twenty-eight (70.0 per cent) of the 40 cases with gangrene had no further loss of tissue substance following lumbar sympathectomy. The process was arrested permanently. Eleven patients obtained no benefit and underwent subsequent amputation.

TABLE VIII. RESPONSE TO LUMBAR SYMPATHECTOMY OF PATIENTS WITH ARTERIOSCLEROTIC GANGRENE

Number of patients	40
No further loss of substance following operation	28
Subsequent amputation	11
Postoperative death	1

Seventy per cent of the 63 patients who underwent sympathectomy obtained degrees of alleviation of symptoms ranging from complete amelioration to slight but significant improvement. Eleven underwent eventual amputation, obtaining no help from sympathectomy (17.5 per cent). There was one death in the series, a mortality rate of 1.6 per cent. It was due to myocardial infarction on the fourteenth postoperative day.

Sympathectomy in Patients With Arteriosclerotic Vascular Insufficiency Associated With Diabetes Mellitus.—There remains little doubt that diabetes mellitus accentuates the natural degenerative changes in the arteries concomitant with advancing age. As previously noted, more than 80 per cent of the 21 cases of diabetes mellitus in this series were poorly controlled, uncontrolled, or undiagnosed at the time of first admission. Table IX presents in detail the general status on admission and the results following lumbar sympathectomy in these diabetic patients after adequate control had been established. The results in this group were surprisingly good. Seventy-six per cent of the results were classified as either excellent or good, comparing favorably with the results of the whole group. Four had subsequent amputation.

The average age of this group of diabetic patients was 54.6 years as compared with 58.2 years for the whole series. The good results obtained in diabetic patients suggest that despite the fact that the more severe arteriosclerotic process produces an earlier onset of symptoms, the arterial tree retains a functional vascular component compatible with its chronologic age.

TABLE IX. DIABETES MELLITUS WITH PERIPHERAL ARTERIOSCLEROSIS OBLITERANS; ANALYSIS OF GENERAL STATUS ON ADMISSION AND RESULT FOLLOWING SYMPATHECTOMY

NO.	AGE (YR.)	SEX	CONTROL	ULCERATION	GANGRENE	RESPONSE TO SYMPATHECTOMY: ULCER	RESPONSE TO SYMPATHECTOMY: GANGRENE	RESULT
1	61	F	Uncontrolled	+ +	+	Healed	Arrested	Excellent
2	63	F	Controlled	Multiple	0	Healed	0	Excellent
3	67	F	Poorly controlled	0	+	Amputation		Poor
4	65	M	Controlled	0	+	Death	P.O.	Death
5	62	M	Poorly controlled	+	+	Improved	Arrested	Good
6	53	M	Poorly controlled	+	+	Healed	Arrested	Excellent
7	58	F	Uncontrolled	+	+	Improved	Arrested	Excellent
8	56	F	Poorly controlled	+	+	Delayed Healing	Arrested	Good
9	60	M	Poorly controlled	+	+	Healed	Arrested	Excellent
10	51	F	Poorly controlled	Multiple	+	Healed	Arrested	Excellent
11	55	F	Uncontrolled	0	+	Mainly prophylactic		Good
12	55	M	Uncontrolled	0	0	Mainly prophylactic		Good
13	71	M	Uncontrolled	+	0	Healed		Excellent
14	54	M	Uncontrolled	+	+	Delayed, healed	Arrested	Excellent
15	69	M	Uncontrolled	+	+	Healed	Amputation	Poor
16	32	M	Uncontrolled	+	+	Delayed, healing	Arrested	Good
17	71	F	Uncontrolled	0	+	Y	Arrested	Excellent
18	75	M	Uncontrolled	+	+	Persisted	Amputated	Poor
19	54	M	Poorly controlled	+	+			Poor
20	56	M	Controlled	+	0	Delayed healing		Good
21	60	F	Controlled	0	+		Arrested	Excellent

The Effect of the Use of Tobacco in Patients With Peripheral Arterial Arteriosclerotic Insufficiency (Table X).—Thirty-six patients were using tobacco in some form when first seen at the hospital. Eight professed to be nonusers, while no reliable record was available in 19. Nineteen patients claimed to have ceased smoking following operation. Eighteen obtained a good or excellent response. Only one patient had a poor result. Two patients refused to stop smoking. One of them was well one year later with an excellent result. The second was adjudged to be in a satisfactory condition one year following sympathectomy that resulted in the arresting of the gangrene.

Of the nonusers of tobacco, excellent results were obtained in 4, another showed improvement in the ulcer and arrested gangrene, while 3 eventually had amputations.

TABLE X. RESULTS OBTAINED FROM LUMBAR SYMPATHECTOMY IN RELATION TO THE USE OF TOBACCO

Using tobacco in some form when first seen		36
Nonusers of tobacco		8
No reliable record		19
Claiming to have ceased smoking after sympathectomy		19
Excellent response	14	
Good response	4	
Poor response	1	
Patients refusing to cease smoking		2
Well one year later with excellent result	1	
Arrested gangrene, condition satisfactory one year later	1	
Nonusers of tobacco		8
Excellent or good results	5	
Subsequent amputations	3	

Although this series is too small to evaluate the effect of tobacco in these patients with arteriosclerotic arterial insufficiency, no significant deleterious effects of tobacco could be observed when smokers and nonsmokers were compared. However, it is of interest to note that 18 out of 19 patients who ceased smoking, following sympathectomy, obtained good results.

DISCUSSION

As stated previously, this group of patients represents individuals with far-advanced arteriosclerotic vascular disease. The routine conservative measures of treatment had been exhausted in many of them. It was not anticipated that all of this group would greatly benefit by operation. It was hoped, by careful study of this "last chance" group of patients, that certain criteria could be obtained as a guide in estimating with reasonable accuracy, patients who could expect beneficial results, those in whom little benefit could be expected, and, lastly, those in whom surgery was contraindicated because of probable unfavorable sequelae.

Greater recognition is being given to the fact that a surprisingly large number of individuals suffering from occlusive disease of the peripheral vessels have a superimposed factor of vasospasm or abnormal vasoconstriction that can be demonstrated by blockade of the lumbar sympathetic chain. It must be clearly established that the term vasospasm infers an abnormal degree of vasoconstriction accompanied by clinical evidence, visual and tactile, of coldness, cyanosis, mottling and sweating, and also a frequent subjective complaint of pain. Vasospasm is an observable and palpable phenomenon whose presence is further verified by demonstrative release of vasoconstrictor tone. The term is greatly misused in the medical literature. Trimble, Cheney, and Moses[7] believed that almost every case of arteriosclerotic peripheral vascular disease has a functional spastic factor. It is also a well-recognized fact that although careful preoperative blocking of the sympathetic chain may provide little or no evidence, that beneficial effects would be obtained from sympathectomy. Subsequent operation, at times, produces a warm foot, an increase in walking distance, and dramatic relief of pain suggesting that even a small improvement in circulation or altered tissue metabolic requirements may change the prognosis considerably. Harris[5] was in accord with this conclusion. He stated that although preoperative tests indicate little or no vasospasm to be present, many cases can be improved by sympathectomy. Such findings suggest that the factor of time plus sympathectomy may produce results not expected from sympathetic block alone.

Vasospasm alone, however, cannot account for all of the beneficial effects obtained by elimination of sympathetic tone. This is substantiated by the observation that often a year is necessary before the maximum benefits of operation will have been obtained. The collateral arterial network will hypertrophy in response to an increase in the volume of blood flow through it. Furthermore, an increase in the volume of blood flow through an ischemic part will follow obliteration of small vessel tone and hypertrophy of the capillary network which may result from release of vasoconstriction after sympathectomy.

Previous reports[1, 2, 3] have emphasized the desirability of demonstrating, prior to sympathectomy, a residual functional component of the arterial tree manifested primarily by increased digital temperature following lumbar block. This is undoubtedly correct in vascular disease in which vasospasm alone is responsible for the patient's symptoms. In the light of our experiences, however, it is felt that in arteriosclerotic vascular disease the importance of the presence or absence of a digital thermal response following lumbar block has been overemphasized. The absence of a digital thermal response is not a contraindication to operation. Rigid adherence to the policy that sympathectomy should be limited to individuals presenting an increased thermal response following lumbar block will exclude many patients in whom beneficial results will follow lumbar ganglionectomy.

Careful study of this group has been done in an attempt to identify indications for, and contraindications to, lumbar sympathectomy. Definite contraindications do exist. They are (1) severe cerebral, cardiac, or renal involvement; (2) paradoxical response to lumbar block, that is, a drop in digital temperature or an aggravation of the patient's symptoms; (3) a rapidly progressing process with widespread arterial involvement; (4) far-advanced atrophy of the involved extremity with skeletization; (5) constant intractable pain.

Indications for sympathectomy exist primarily in the lack of contraindication to operation. The following are important, nevertheless, in selecting suitable patients: (1) subjective or objective response to lumbar sympathetic block; (2) lack of widespread arterial involvement with slowly progressive vascular changes; (3) prophylaxis in patients with contralateral amputation. This is now being done routinely in cases in which specific contraindications do not exist; (4) as a measure of last resort after other forms of therapy have failed to arrest the process.

Sympathectomy has proved to be a relatively safe operation in this group of patients who are usually considered poor surgical risks. Only one death has occurred in 63 operations, a mortality rate of 1.6 per cent. Complications, the majority of which are peculiar to sympathectomy in arteriosclerotic vascular insufficiency, were observed in 14 patients.

Vascular Complications (Table XI).—Death occurred on the fourteenth postoperative day in one patient from acute myocardial infarction. A second patient had an exacerbation of known coronary occlusive disease following operation. His condition one year later was satisfactory.

TABLE XI. COMPLICATIONS AND SEQUELAE TO LUMBAR SYMPATHECTOMY FOR ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Vascular		2
(1) Death 14 postoperative days from myocardial infarction	1	
(2) Exacerbation of known coronary disease; patient's condition satisfactory 1 yr. later	1	
Severe wound infection		5
Paradoxical gangrene		2
Delayed congestive syndrome		5
Postoperative neuralgia, frequent		

Wound Infection.—Severe wound infections complicated five cases. Four out of five of these patients had diabetes mellitus with ulceration and gangrene.

Paradoxical Gangrene.—Atlas[1, 2] has called attention to the occlusal rapid onset of gangrene following sympathectomy. This phenomenon has also been commented upon extensively by Freeeman, Leeds, and Gardner.[9] Two mechanisms are thought to operate simultaneously in the augmentation of the ischemia and resultant gangrene in these cases: (1) Due to destruction of the vasomotor control over the arteriovenous anastomoses in the skin, there is diversion of blood directly from the arterial to the venous side of the anastomosis without passing into the distal capillary beds. Although there may be a rise in skin temperature, actually there results a decrease in the nutrient capillary flow; (2) obliteration of vascular tone results in lowering of the effective pressure necessary to drive blood into the nutrient capillaries by decreasing peripheral resistance.

We have observed gangrene with rapid onset following sympathectomy in two cases. One case came to amputation. In the second, the gangrenous process underwent spontaneous arrest. Amputation was not necessary and the ultimate result was considered satisfactory.

Delayed Congestive Syndrome.—Five patients developed a delayed swelling of the sympathectomized leg not unlike the clinical picture presented by chronic thrombophlebitis. This peculiar syndrome is prone to develop following sympathectomy in patients with arteriosclerosis obliterans who also have clinically evident phlebosclerosis. The superficial veins are more apparent in this type of patient, but are not necessarily varicose veins. Following sympathectomy, over a period of one to three months, the patient develops congestive phenomena. This is characterized by a soft pitting edema and early stasis changes involving the lower part of the leg. The direction of flow in the superficial sclerotic veins is rapidly upward. The impression is gained that the arterial inflow and venous return are minimally disproportionate. Supportive therapy consisting of rest, elevation, and compression bandages fails to relieve the patient. The condition slowly regresses as the sclerotic veins become better able to return the increased flow into the leg. Patients who have developed this peculiar congestive syndrome have had good results from sympathectomy in 3 of the 5 cases. Two had poor results, subsequent amputation being necessary.

Postoperative Neuralgia.—A neuralgic type of pain involving the posterior and lateral aspects of the thigh of the sympathectomized leg has been observed in occasional patients in this series. Onset of the pain occurs during the first seven postoperative days. It is constant, severe, and prevents the patient from sleeping. It has been described as more severe than rest pain or intermittent claudication. Fortunately, the duration of this complication has never been observed to be greater than two weeks. It responds satisfactorily to bed rest and analgesics. This phenomenon is apparently due to irritation of sensory nerves innervating these skin areas. The mechanism whereby these nerves are abnormally stimulated is not always evident but the most probable cause is operative trauma.

SUMMARY

1. The early results of 63 patients submitted to lumbar sympathectomy for far-advanced obliterative arteriosclerotic vascular disease have been presented.

2. Follow-up studies over a two and one-half year period reveal that 70 per cent of the group obtained some measure of alleviation of symptoms following operation.

3. Indications for, and contraindications to, sympathectomy in this group of patients have been presented and discussed. It is not possible to establish indications for operation by statistical methods. Great care must be exercised in choice of patients if good results are to be consistently obtained.

4. The deleterious effects of sympathectomy for arteriosclerotic vascular insufficiency have been noted and discussed.

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THE ARTERIOSCLEROTIC POPLITEAL ANEURYSM

A Report of Fourteen Patients Treated by a Preliminary Lumbar Sympathetic Ganglionectomy and Aneurysmectomy

Robert R. Linton, M.D. Boston, Mass.

(From the Departments of Surgery of the Massachusetts General Hospital and the Harvard Medical School)

SPONTANEOUS aneurysms of the popliteal artery are the most common aneurysms which are curable by surgical measures. The true incidence of this disease is probably not given in any available statistics, but according to Crisp[1] this blood vessel was involved more frequently than any other artery of the body except the thoracic aorta. In a series of 551 cases of aneurysm he collected in 1847 he found that 137, or 25 per cent, were of the popliteal artery, whereas 175, or 32 per cent, were of the thoracic aorta, the most common site of aneurysm in the body. Matas[2] in 1920 reported the involvement of the popliteal artery in 154, or 53.2 per cent, of 289 cases of aneurysm which had been operated upon by his technique of endoaneurysmorrhaphy.

Syphilis plays an important role in the etiology of some aneurysms, but many instances are encountered without evidence of this disease in which arteriosclerosis is the chief etiological factor. The luetic type of aneurysm occurs usually in patients under the age of 50 years, whereas the arteriosclerotic more frequently in those past the age of 60 years. The reports in the surgical literature, except for Lilly's[3] recent one, have not directed particular attention to the arteriosclerotic type of aneurysm. In a group of 42 patients admitted to the surgical wards of the Massachusetts General Hospital for the forty-year period from 1908 to 1947, arteriosclerosis was the chief etiological factor in 31, or approximately 74 per cent, of the cases. It also played a role, undoubtedly, in 4 of the patients with lues, whose ages were 57, 57, 58, and 66 years. An analysis of this group of 42 patients reveals that the luetic type has been occurring less frequently, whereas the arteriosclerotic is becoming more common. In the first decade of this period from 1908 to 1917, there were 4 syphilitic aneurysms and no arteriosclerotic ones. In the next decade, 1918 to 1927, there were 4 cases; 1, or 25 per cent, was arteriosclerotic, and 3, or 75 per cent, were luetic. From 1928 to 1937, 9 patients were seen; 5, or 55 per cent, were arteriosclerotic and 4, or 45 per cent, were luetic. During the last decade, 1938 to 1947, it is of extreme interest that 25 patients were seen, and all, or 100 per cent, of them were arteriosclerotic; none were luetic (Fig. 1). The ages in the arteriosclerotic group ranged from 43 to 82 years, with a mean age of 65 years, while in the luetic group they were from 30 to 66 years, with a mean age of 47.7 years. Tabulated in decades according to years in the

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arteriosclerotic group, 3 were in the fifth decade, 6 in the sixth, 10 in the seventh, 11 in the eighth, and 1 in the ninth, whereas in the luetic group 4 were in the fourth decade, 2 in the fifth, 4 in the sixth, and 1 in the seventh (Fig. 2). This increased incidence of the arteriosclerotic popliteal aneurysm, especially during the last decade, 1938 to 1947, is apparently due to the fact that the span of human life is increasing, and people are living to an older age, when they

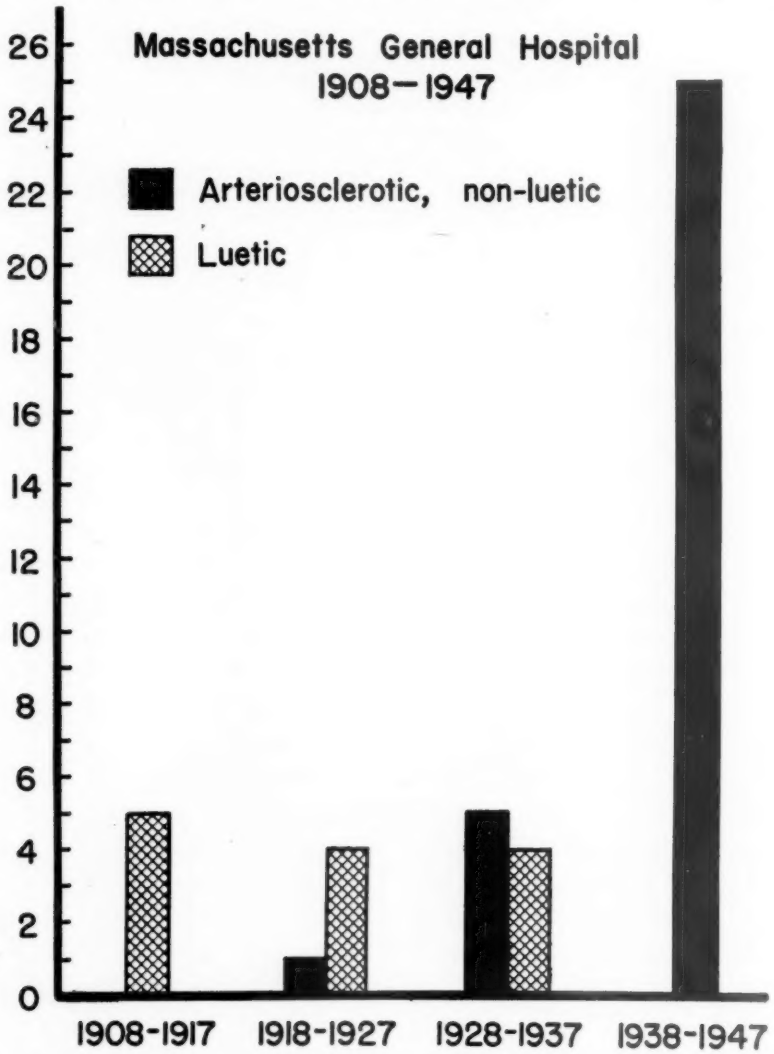


Fig. 1.—Graph showing incidence of arteriosclerotic and luetic popliteal aneurysms in 42 patients admitted to the Massachusetts General Hospital in the forty-year period from 1908 to 1947 and arranged according to decades.

are more subject to degenerative vascular diseases. According to Ivy,[4] the life expectancy in 1900 was 49 years, whereas in 1945 it was 66 years. He also pointed out that 7.7 per cent of the population in the United States, or almost 11 million persons, are now over 65 years of age, and by 1960, there will be 9 per cent over this age. It seems, therefore, from these statistics that this type of vascular lesion will be seen with a still increasing frequency.

The surgical treatment of aneurysms dates back many centuries. Antyllus, a Roman surgeon in the third century, according to Henry,[5] and the fourth century according to Treves,[6] developed the method of tying the artery above and below the aneurysmal sac and then evacuating the contents. Philagrius of Macedon in the fourth century, according to Ransahoff,[7] first practiced extirpation of an aneurysm. Guthrie,[8] writing in 1830, stated that Aetius in the sixth century recommended ligation and division of the artery proximal to the aneurysm, then opening of the sac and intrasaccular ligation of the artery at the distal end of the sac. The same author stated that Paulus in the

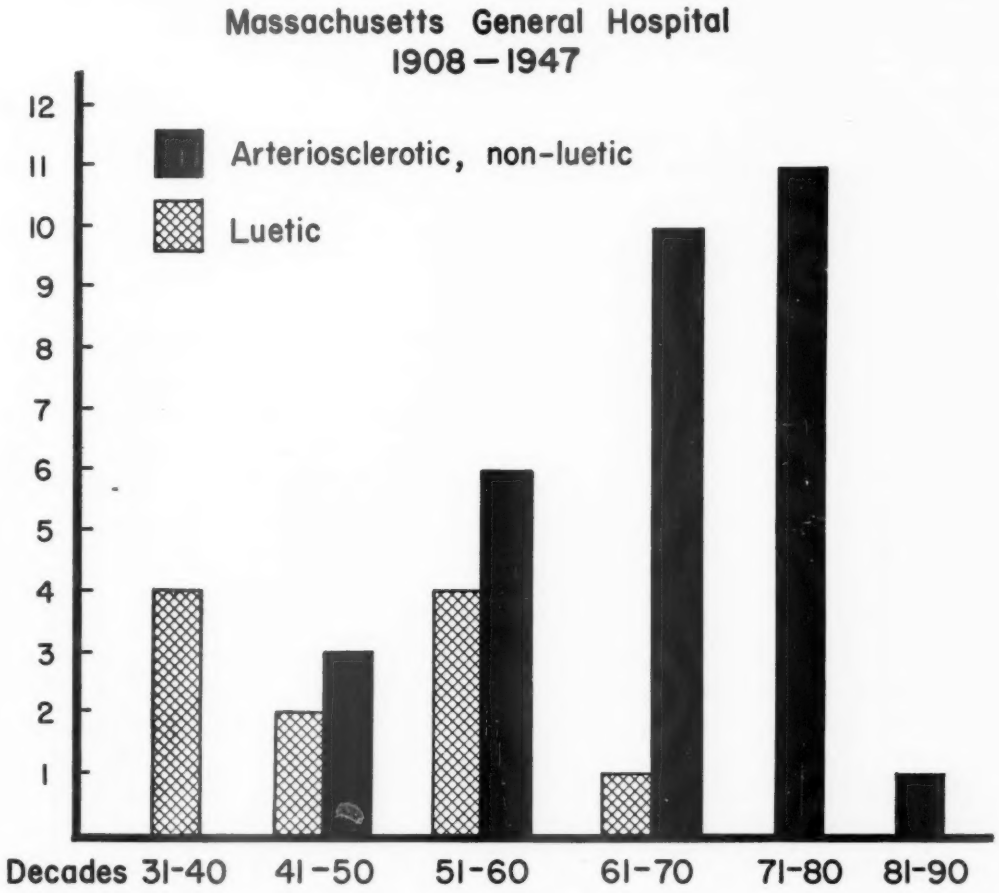


Fig. 2.—Graph showing ages in years, arranged according to decades, of 42 patients with arteriosclerotic and luetic popliteal aneurysms admitted to the Massachusetts General Hospital in the forty-year period from 1908 to 1947.

seventh century advised extirpation of the aneurysm, having previously applied a ligature above and below it. Surgery of aneurysms, according to Guthrie,[8] remained in this state until the sixteenth century, when Guillemeau advised proximal ligation, opening of the sac, removing the intrasaccular thrombi and filling it with lint, leaving it to heal by the usual processes of suppuration and cicatrization. Purmann, in the seventeenth century, according to Ransahoff,[7] rediscovered the method of treatment by extirpation, first described by Philagrius. Anel, in the sixteenth century, according to Ottley,[9]

tied the artery immediately above the sac but left it unopened. Hunter, in the eighteenth century, developed his method of proximal ligation some distance from the sac in what is now known as Hunter's canal for the treatment of popliteal aneurysms. His method was first described by his assistant, Home, in 1786[10] and again in 1793.[11] Again the surgery of aneurysms remained in this state until Matas,[12] in the first part of the twentieth century, described his method of endoaneurysmorrhaphy which since then has been considered the standard method of treatment. He was the first to stress the importance of building up the collateral circulation before operating on the aneurysm. According to Matas,[13] gangrene followed the Hunterian operation, or proximal ligation, in 10.5 per cent of the cases; the Antylus' method, or proximal and distal ligation with evacuation of the sac, in 8.33 per cent; the Philagrius' or Purmann's method of extirpation of the sac in 5.71 per cent. Matas,[2] in 1920, reviewing 154 cases of popliteal aneurysm treated by his method of endoaneurysmorrhaphy, reported an incidence of gangrene in 8 cases, or 5.2 per cent. From these statistics it is apparent that regardless of which method was used to cure a popliteal aneurysm, a certain number of extremities developed gangrene. It was natural, therefore, that some other method of treatment should be sought for to eliminate it in all the cases if possible.

The next important advance in the surgical treatment of aneurysms resulted from the experimental work of Mulvihill and Harvey[14] in 1931, when they demonstrated the beneficial effect of sympathetic ganglionectomy to the extremity after acute arterial occlusion. Gage[15] in 1934 was the first to utilize this method in the treatment of an aneurysm of the common iliac artery. Bird[16] in 1935 reported the first popliteal aneurysm treated with success by a preliminary lumbar sympathetic ganglionectomy followed in four weeks by an obliterative endoaneurysmorrhaphy. Since then others have confirmed the beneficial results obtained by preliminary sympathetic ganglionectomy in the treatment of aneurysms of the lower extremity. Leriche and Froehlich[17] in 1939 utilized it in an occluded aneurysm of the femoral artery. Gage[18] in 1940 reported its use in 15 cases of aneurysmorrhaphy and again in 1943[19] recommended it in the management of traumatic arterial aneurysms. Richards and Learmonth[20] in 1942 performed a lumbar sympathectomy three weeks prior to extirpation of a popliteal aneurysm with success. Lilly[3] in 1946 reported 3 popliteal aneurysms treated successfully by sympathectomy and aneurysmorrhaphy.

The purpose of this paper is to report 14 patients with arteriosclerotic type of popliteal aneurysm admitted to the surgical wards of the Massachusetts General Hospital during the five-year period 1942 to 1947 and to describe the method of treatment utilizing a two-stage operative procedure, first a preliminary lumbar sympathetic ganglionectomy and later an aneurysmectomy. The ages of these 14 patients ranged from 49 years, the youngest, to 79 years, the oldest. The mean age was 65 years. One patient was in the fifth decade, aged 49 years; 3 were in the sixth decade, aged 53, 54, and 56 years; 5 were in the seventh decade, aged 61, 63, 64, 68, and 69 years; 5 were in the eighth

decade, aged 71, 74, 74, 75, and 79 years. There were 13 men and 1 woman in this group of patients. The aneurysms were unilateral in all the patients except one in whom they were bilateral, so that there were a total of 15 in the 14 patients, 7 in the right extremity and 8 in the left. The one patient with bilateral aneurysms lost the right leg from gangrene because of thrombosis of the aneurysm before surgical measures could be instituted to save it. For that reason this aneurysm will not be considered further in this report. Aneurysms devoloped spontaneously in 11 patients and followed trauma in 3 of them. One patient gave a history of a severe fall and wrenched knee two weeks before the aneurysm was noticed; another had dislocated his knee seven years previously and the other had received a severe blow four months prior in the popliteal space. Syphilis did not play a role in the etiology of any, since the blood Hinton or Wassermann tests were negative in all the patients. Swelling in the popliteal space had been noted by 11 patients and was unobserved by 3. The duration that the aneurysms had been noted by the patients varied from one week to five years. In the majority it was eight weeks or less. The predominant symptom and complaint was local pain in the popliteal space observed in 11 patients. The other 3 were not conscious of the aneurysm and did not complain of pain. These were detected in routine examinations of their extremities. The pain developed suddenly in 4 instances secondary to a sudden increase in the size of the aneurysm, and in 2 cases as the result of a rupture of the sac with the formation of a false aneurysm. The size of the aneurysmal sac varied from 3 by 5 cm., the smallest, to 15 by 20, the largest. Twelve were fusiform in shape and 2 were saccular with large associated false aneurysms. Arterial pulsations were detectable in all the aneurysms and, in addition, in the dorsalis pedis artery in 4 of the extremities, and in the posterior tibial artery in 6 instances. All 3 of these arterial pulsations were present in 2 of the extremities. Intermittent claudication was a symptom in 4 patients, varying from one to ten years in duration. These observations indicate that in most of the patients there was evidence of obliterative arterial disease distal to the aneurysm, but none showed any evidence of gangrene in the extremities. Pathologic examination of all the aneurysms revealed a laminated blood clot consisting of partially organized and fresh thrombi (Fig. 3). In most instances some of it was so loosely attached that if it had been dislodged, embolism of the arteries distal to the aneurysm would have occurred with resulting gangrene of the extremity.

The aneurysmectomies were performed seven to eleven days after the sympathectomies. Gangrene of the extremity did not develop in any of the cases and only in one instance did the circulation seem precarious for a few days following the aneurysmectomy. Intermittent venous occlusion[21] was used in this instance until the circulation was adequate. This patient was aged 74 years. There were pulsations in the dorsalis pedis and posterior tibial arteries before operation, indicating that the collateral circulation of the lower leg and foot had not developed to the extent that it had in most of the other patients, whose peripheral arteries had been previously occluded due to

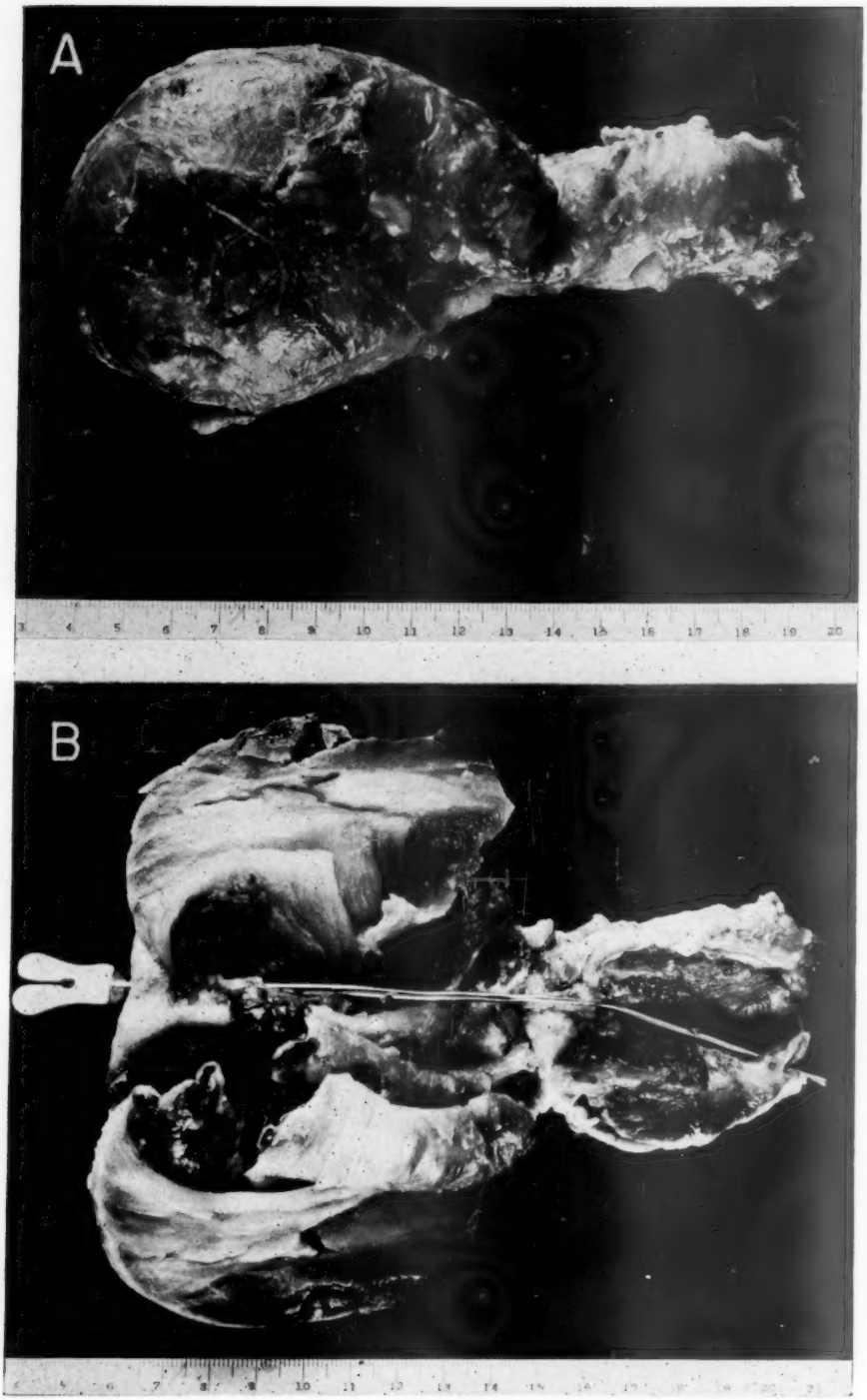


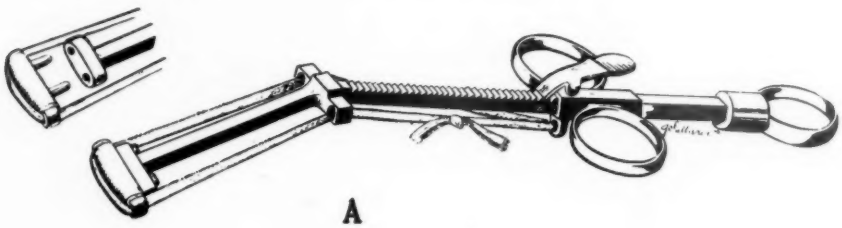
Fig. 3.—*A*, Photograph of a double arteriosclerotic popliteal aneurysm removed from a man aged 71 years. Note how clean the aneurysm has been resected. *B*, Photograph of the same specimen opened, showing the old partially organized and fresh thrombi almost filling the aneurysmal sac. The latter, if dislodged, may produce embolism of the distal arteries with resulting gangrene of the extremity.

arteriosclerosis, so that the sudden surgical occlusion of the popliteal artery at the time of the aneurysmectomy reduced the circulation distal to this point to a precarious level. It is believed that without the preliminary sympathectomy the extremity probably would have developed gangrene. One patient died following the lumbar sympathectomy, a mortality rate of 7 per cent. The cause of death in this case was a combination of postoperative retroperitoneal hemorrhage and heart failure from severe coronary heart disease. The former was thought, in part at least, to be attributable to the postoperative use of intravenous heparin to prevent thrombosis of the popliteal aneurysm after the sympathectomy. Since then in other patients it has not been used following the sympathectomy. This patient was a poor selection for the operation, because the post-mortem examination showed a previous coronary thrombosis had caused a severe infarction of the left ventricle. None of the 13 patients who survived the operative procedures developed gangrene and both the life of the patient and the limb were preserved in all cases, or 93 per cent of the entire group.

The method of treatment that is recommended is a two-stage operative procedure to include a preliminary lumbar sympathetic ganglionectomy, which is followed in approximately ten days by an aneurysmectomy. Certain points in the operative management of these cases by this method need particular emphasis. A careful evaluation of the patient's cardiovascular condition is imperative and should be done before the sympathectomy. The staging of the operative procedures is of extreme importance because it permits the interruption of the popliteal artery, after elimination of the vasoconstrictor influence of the sympathetic nervous system and after stabilization of the vascular system in its maximum degree of vasodilatation, as demonstrated by Smithwick.[22] Furthermore, both procedures should not be done at the same operation because of the danger of surgical shock with a drop in the arterial blood pressure. Even if the patient survived, the extremity would likely suffer irreversible vascular changes with resulting gangrene because the degree of hypotension distal to the interruption of the popliteal artery would be relatively greater than in the remainder of the arterial system. Ether inhalation anesthesia was used for the lumbar sympathetic ganglionectomy, since it is considered the safest method in these elderly arteriosclerotic patients. Spinal anesthesia was used preferably for the aneurysmectomy, because with the low level of anesthesia required for operating at the knee the patient's systemic blood pressure could be more readily maintained than with a general anesthetic. In addition, the vasoconstricting influence of ether anesthesia on an extremity previously sympathectomized was eliminated. The sympathectomy was performed through an extraperitoneal exposure. The flank type of incision described by Smithwick[23] was used to facilitate the removal of the first, second, and third lumbar ganglia so that the entire thigh as well as the lower leg would be sympathectomized.

A limb tourniquet should not be used to control the arterial inflow to the extremity: First, because of the danger of fracturing an arteriosclerotic femoral

artery. Second, it shuts off all the arterial inflow to the extremity during the operation so that the collateral arteries in the operative field are not readily recognized and preserved. Third, on release of the tourniquet, the state of so-called "tourniquet shock" may develop with a drop in the systemic blood pressure which would be serious to both the patient and the limb. The application of a modified Bethune lung tourniquet clamp (Fig. 4) to the popliteal artery proximal and distal to the aneurysm was utilized for the control of the arterial inflow to the aneurysm. This method of arterial control is recommended for a number of reasons. First, it gives the surgeon peace of mind to perform a careful dissection close to the aneurysm so that the collateral arteries



A

B

Fig. 4.—The author's modification of the Bethune lung tourniquet clamp. *A*, The standard Bethune clamp modified by angulating the shank. The inset shows a wider end piece which may be inserted into the end of the regular clamp. The advantage of this is that it prevents puckering of the wall of a large blood vessel. *B*, A specially constructed stainless steel tourniquet clamp with a wide end piece. Note the end piece is slightly convex and covered with cloth. The convexity gives better hemostasis and the fabric covering prevents the blood vessel from slipping without applying too great a pressure to it. The tourniquet used is a narrow white shoe lace.

will not be damaged, since uncontrollable hemorrhage will not occur even if the aneurysmal sac is inadvertently opened. Second, with the main arterial inflow to the aneurysm shut off both proximally and distally, a thrombus from it, if dislodged during the further dissection of the sac, will not be carried distalward to occlude the arterial system. Third, the collateral blood supply about the knee and to the lower leg and foot is not shut off during the operation so that necessity for haste during the dissection is eliminated. Fourth, the collateral arteries in the operative field since they still pulsate can be recognized and preserved. Fifth, the so-called "tourniquet shock," which may develop after the removal of a tourniquet applied to the thigh, does not

occur because blood still can circulate through the collateral channels, the same ones that the limb will depend on thereafter for its circulation. Sixth, the observation of arterial bleeding from the distal end of the popliteal artery after extirpation of the aneurysm, the so-called Henle-Coenen sign, will demonstrate to the surgeon the adequacy of the collateral circulation and assure him of the viability of the extremity.

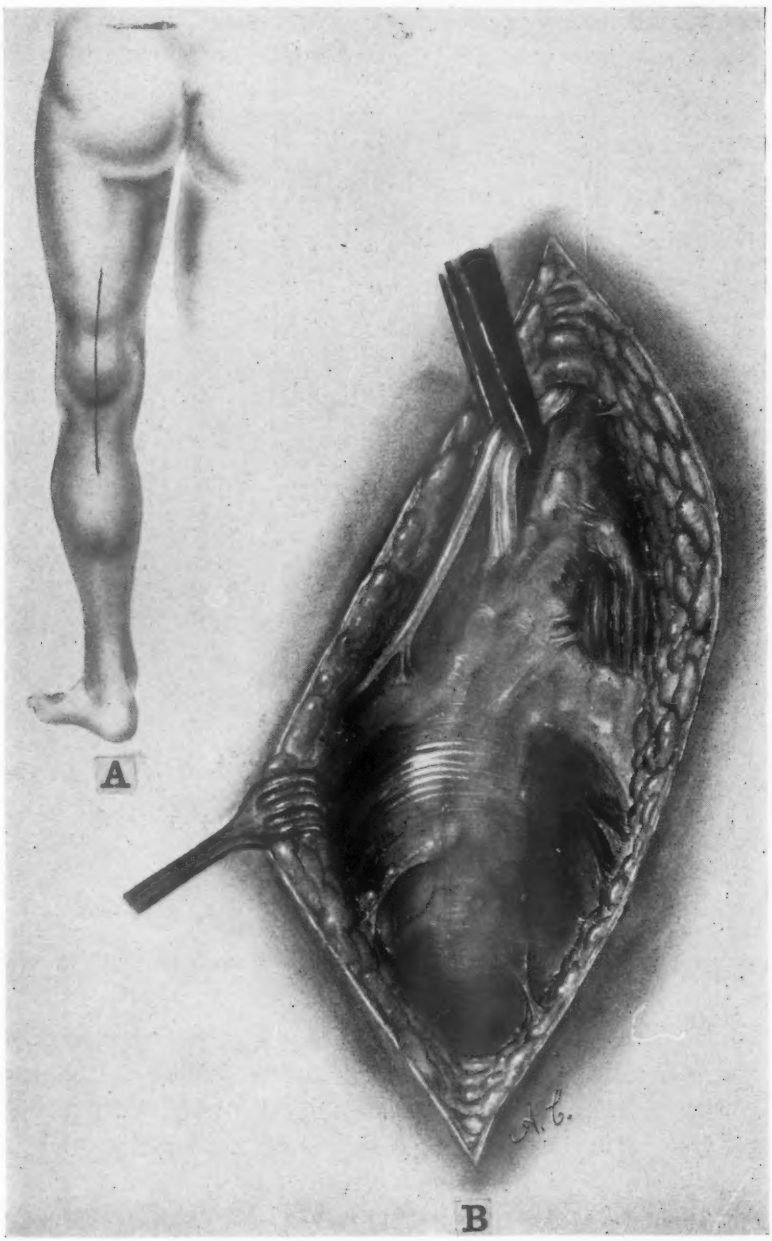


Fig. 5.—An artist's drawing showing (*A*) the long vertical type of incision, extending sufficiently proximal and distal to the aneurysm to give easy access to the afferent and efferent blood supply and (*B*) the first step in isolating the sciatic, posterior tibial, and peroneal nerves in order to avoid damage to them.

Adequate exposure of the aneurysm, its main afferent and efferent arteries, is essential and cannot be overemphasized. It is best obtained by an incision which overlies and parallels these blood vessels. For these reasons a vertical incision is recommended, which extends proximal to the anuerysm into the thigh, and distal to it into the upper part of the lower leg (Fig. 5). The crease in the popliteal space is necessarily crossed by the incision, but with careful closure of it, using fine nonabsorbable interrupted sutures to the popliteal fascia and interrupted vertical mattress sutures to the skin, contractures or keloid scars have been avoided in all the extremities (Fig. 6).

Fig. 6.—A photograph showing a healed vertical type of incision, without contracture or keloid formation, in a patient 71 years old, taken five years after the aneurysmectomy.

When the incision is completed, towels are sutured to the skin edges to isolate the operative field from skin contamination during the operation. The great nerves, the sciatic, common peroneal, and posterior tibial nerves, are first dissected free. The latter is often intimately attached to the aneurysmal sac. After isolating them a soft, wide, thin rubber band is placed around each to mark them for retraction is necessary during the further dissection (Fig. 5). If these precautions are not taken the nerves may be injured by retractors with resulting partial paralysis. Next, the popliteal artery is exposed proximal to the aneurysm between the biceps femoris and the semimembranosus

muscles. Great care is taken not to damage the superior genicular arteries if they arise above the aneurysm, and also the highest genicular artery, which arises from the distal part of the superficial femoral artery. Modified Bethune lung tourniquet clamps (Fig. 7) are applied to the popliteal artery about 2 cm. proximal and distal to the aneurysm and the vessels occluded during the remainder of the dissection. The aneurysmal sac is dissected free with extreme

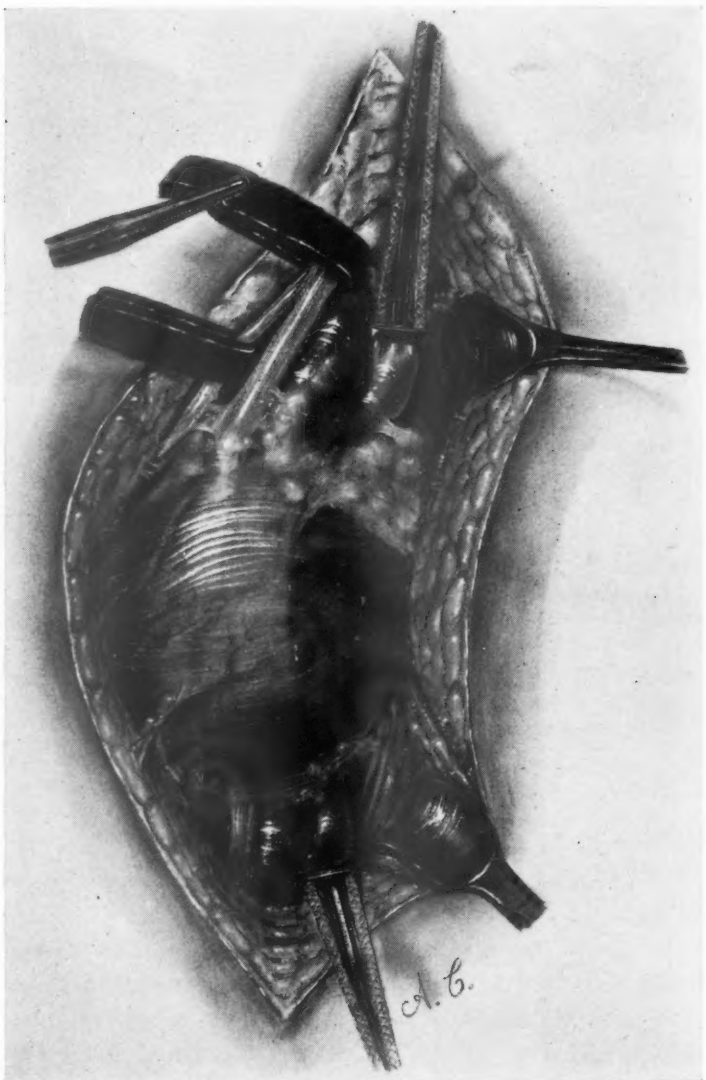


Fig. 7.—An artist's drawing showing the aneurysm, the sciatic, common peroneal, and posterior tibial nerves. The latter retracted with wide but thin rubber bands. Note the tourniquet clamps on the popliteal artery proximal and distal to the anuerysm. The popliteal vein lies on the aneurysmal sac, to which it is intimately attached.

care, staying as close to it as possible by developing a cleavage plane between it and the tissues of the popliteal space. In this manner the tributaries arising from the aneurysm may be ligated at their origin and the arteries of the collateral blood supply will not be damaged any more than if they were ligated

by the intrasaccular method. The popliteal vein as a rule is intimately adherent and sometimes incorporated in the posterior wall of the aneurysm (Fig. 7). No attempt should be made to preserve it unless it lies free, as occasionally is the case with a very small aneurysm arising from the anterior wall of the popliteal artery. This is contrary to Matas' advice[13] as he stated, "I believe that preservation of the (popliteal) vein is a matter of decided importance to the viability of the limb, and its sacrifice when unavoidable must always be a source of anxiety and apprehension." There seems little support to this view in the cases of this report, since the popliteal vein was resected in 12 of them without serious effect to the extremities. In the remaining one, it lay free of a small aneurysm, so it was not interrupted but the superficial femoral vein was interrupted to prevent thromboembolism.

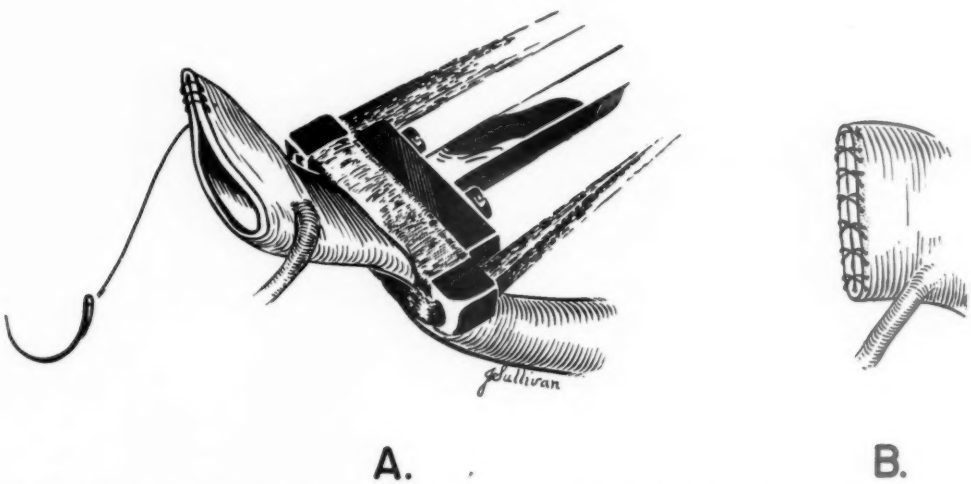


Fig. 8.—An artist's drawing showing the suture method of closing the popliteal artery to preserve a collateral artery. *A*, The tourniquet clamp is still closed, with the over-and-over suture started. *B*, The closure completed with a double row of sutures, with preservation of the collateral artery.

The next step is to ligate the proximal and distal ends of the popliteal artery and vein. This should be performed with nonabsorbable ligature material, first ligating the vessel and then placing a transfixion ligature in the cuff distal to the primary ligature. An alternate method of closing either or both ends of the popliteal artery has been used to preserve collateral arteries that arise within 1 cm. of them. Adequate hemostasis under these circumstances is obtained by closing the end of the popliteal artery with two rows of a running suture of 0000 arterial silk, a method similar to the one described by Murray and Janes[24] (Fig. 8). In this manner the collateral vessel may be saved, since only 1 to 2 mm. of the popliteal artery are used, whereas with the usual ligature closure about 1 cm. is necessary, which would also occlude the collateral artery. After a final inspection of the great nerves and blood vessels, the wound is closed in two layers without drainage (Fig. 9). Interrupted sutures of fine silk or cotton are used in the popliteal fascia and the skin is closed with interrupted vertical mattress sutures of silk. This latter

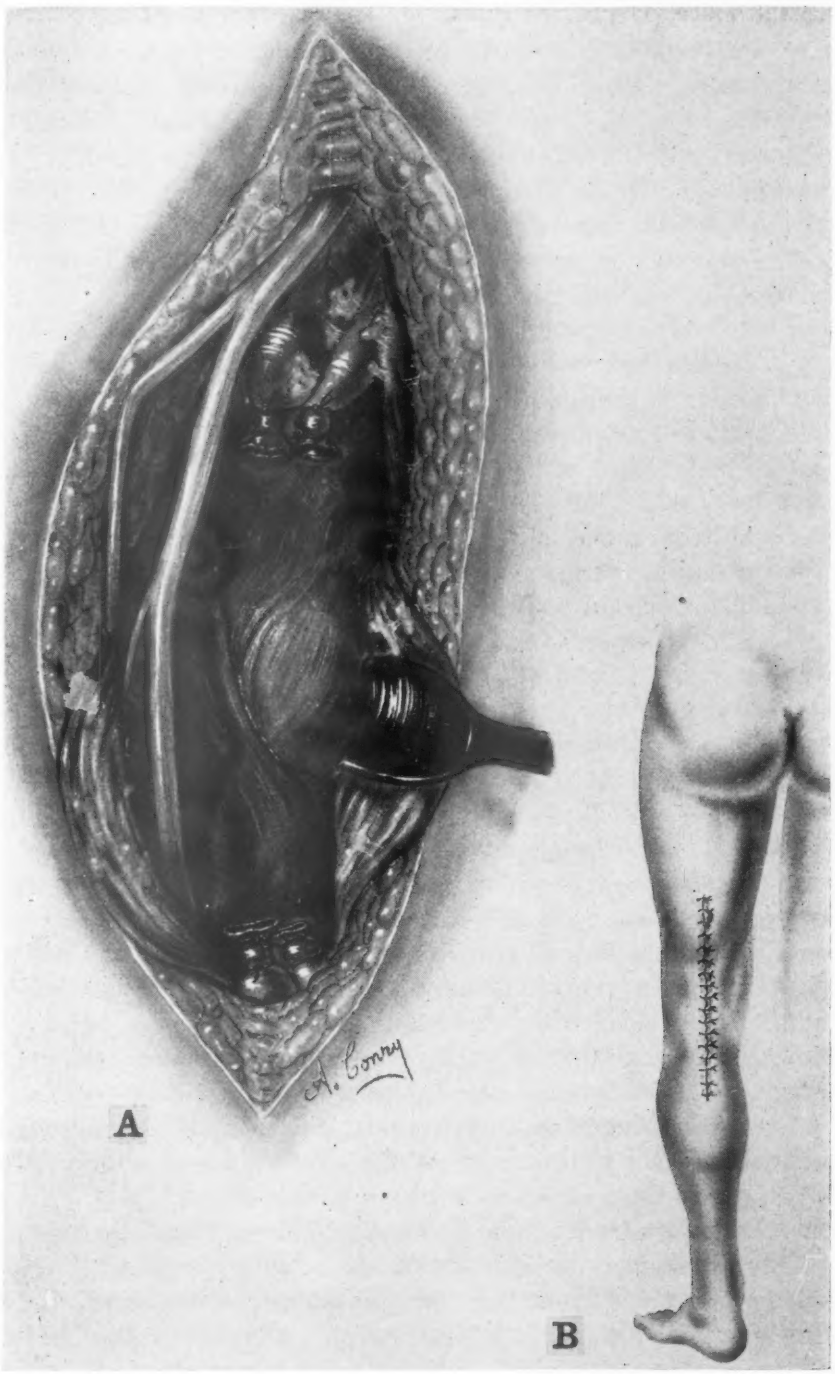


Fig. 9.—An artist's drawings to show (*A*) the operative field with the aneurysm removed, the great nerves intact, the proximal and distal ends of the popliteal artery and vein doubly ligated, and (*B*) the incision closed without drainage with fine interrupted cotton or silk sutures to the popliteal fascia and interrupted vertical mattress silk sutures to the skin.

type of suture is important to prevent a contracture in the scar at the crease in the popliteal space, as previously stated. A posterior molded plaster splint is applied to the thigh and lower leg to keep the knee in extension. Bilateral superficial femoral vein interruptions are recommended in these patients to prevent pulmonary embolism. These should be performed preferably before the aneurysmectomy, but they may also be done a day or two after it. Intravenous heparin may be used for a few days following the removal of the aneurysm to prevent arterial thrombosis in the arteries distal to the knee. The decision whether or not to use this drug depends on the degree of the collateral circulation; that is, if it is poor it is advisable to use the drug, whereas if it is excellent the drug is not necessary. Following the operation the patient is placed in bed, the head of which has been elevated about six inches on blocks in order to keep the extremity a little below the level of the heart to insure a better circulation of the foot. In addition, it should be kept cool to maintain the metabolism of the leg at a lower level consistent with the diminished arterial blood supply. External heat should not be applied to the lower leg and foot under any circumstances. The patients are ambulatory usually by the end of the first week and are discharged home from the hospital at the end of the second week.

DISCUSSION

Many surgeons believe that the surgical interruption of the popliteal artery, as is necessary in the excision of a popliteal aneurysm, may result in gangrene of the extremity. This opinion is based chiefly on the experiences of major blood vessel injuries occurring in World War I and World War II, since it was observed that the popliteal artery if injured resulted in a higher incidence of gangrene than any other peripheral artery. DeBakey and Simeone[26] reported that in a collection series of 502 popliteal artery injuries from American World War II casualties, there were 364, or 72.5 per cent, who lost limbs. They also reported that Ogilvie of the British Army Medical Corps stated at the Cairo Conference in 1943 that he had not seen in the course of war a single instance of ligation of the popliteal artery which was not followed by gangrene. It is to be emphasized, however, that conclusions regarding the results of elective surgery on the popliteal artery, such as reported here for aneurysms, should not be drawn from the experiences of gunshot wounds of this vessel. An analysis of the two types of wounds, the one resulting from a missile and the other from a surgeon's scalpel, reveals little analogy. There is usually with the former, in addition to the popliteal artery injury, a severe wound of the soft parts about the knee joint with destruction of the collateral blood vessels or occlusion of them from edema and extravasation of the blood, whereas the ligation and division of it, even the extirpation of the aneurysm, leaves these vessels intact for the most part so that gangrene rarely will occur. Furthermore, a preliminary sympathectomy in cases of elective major blood vessel surgery as described here can be performed to safeguard the extremity, thereby preventing vascoconstriction of the arterial system distal to the point of the arterial interruption.

Excision of an aneurysm is one of the oldest methods of surgical treatment for this condition. Philagrius of Macedon[7] in the fourth century first practiced it, then it was discarded but later rediscovered by Paulus[8] in the seventh century and by Purmann[7] in the seventeenth century. It had many advocates in the nineteenth century until Matas[12] described his method of endoaneurysmorrhaphy at the beginning of the twentieth century. Now, again, it is recommended as the most satisfactory method of treatment for the arteriosclerotic type of popliteal aneurysm, when it is combined with a preliminary sympathetic ganglionectomy. Extirpation of the aneurysm is preferred in this type to the Matas obliterative endoaneurysmorrhaphy, because of the difficulty encountered frequently in obliterating the aneurysmal sac due to the rigidity of its walls from arteriosclerosis and calcification. It is considered also to be a safer method for this type of aneurysm than the ingenious restorative endoaneurysmorrhaphy by a veingraft inlay, described recently by Blakemore,[25] because of the marked arteriosclerosis of the popliteal artery both proximal and distal to the aneurysm, which makes a satisfactory nonsuture type of anastomosis difficult to perform.

It is believed that any patient presenting an arteriosclerotic popliteal aneurysm irrespective of age should be considered a candidate for the surgical removal of it, preferably by a preliminary sympathectomy and followed later by an aneurysmectomy, unless the patient's cardiac condition contraindicates such treatment, or if the aneurysm has become thrombosed spontaneously with resulting gangrene of the extremity. The presence of multiple aneurysms of a similar nature in other large arteries of the body may also be a contraindication. The serious effect of this condition on the life of the patient and the extremity in untreated cases, it is believed, makes this radical view justifiable. It is well demonstrated by the outcome in a group of 15 patients similiar to the one in this report, who were admitted to the Massachusetts General Hospital from 1929 to 1947 because of unilateral or bilateral arteriosclerotic popliteal aneurysms that were not treated by surgery. The mean age of this group was 66.7 years; the youngest patient was aged 48 years and the oldest was 82 years. Seven of the patients had bilateral aneurysms, making a total of 22 extremities with popliteal aneurysms. Eleven patients, or 50 per cent, had gangrene of the extremities on admission to the hospital and another 6 or 27 per cent, developed it in the hospital while awaiting surgery. Low thigh amputations were performed on all 17 extremities, making a limb mortality of 77 per cent. This dire effect to the extremity in untreated cases has been emphasized recently in the literature by others, including Blakemore,[27] Flemming,[28] Hufnagel,[29] Keynes and Morel,[30] Lilly,[3] Theis,[31] and Wells and associates.[32] Furthermore, a patient mortality rate of 26.6 per cent occurred, since 4 patients died as a result of the disease following amputation of an extremity, performed because of gangrene secondary to thrombosis of the aneurysm; 1 died from septicemia, and the other 3 from massive pulmonary embolism. The results obtained in the 14 similar cases of arteriosclerotic popliteal aneurysm in this report, treated by a preliminary sympathetic ganglionectomy and aneurysmectomy,

demonstrate what can be accomplished with modern surgical treatment. Thirteen patients and their extremities survived, a salvage of 93 per cent without evidence of gangrene. One patient died following the sympathectomy, a mortality rate of 7 per cent.

A follow-up study reveals that two of the patients have died, one from cirrhosis of the liver one year later and the other after fourteen months from the rupture of an arteriosclerotic common iliac aneurysm. The extremities of all these patients functioned normally following the operative procedure. Eleven of them are still living and well two months to five years since discharge from the hospital. The most common postoperative complication was edema of the lower leg which developed in 5, or 38 per cent, of the cases. It disappeared in 3 of them with elastic bandages; the other 2 still need some support to the extremities. It is of extreme interest that the arterial inflow to the

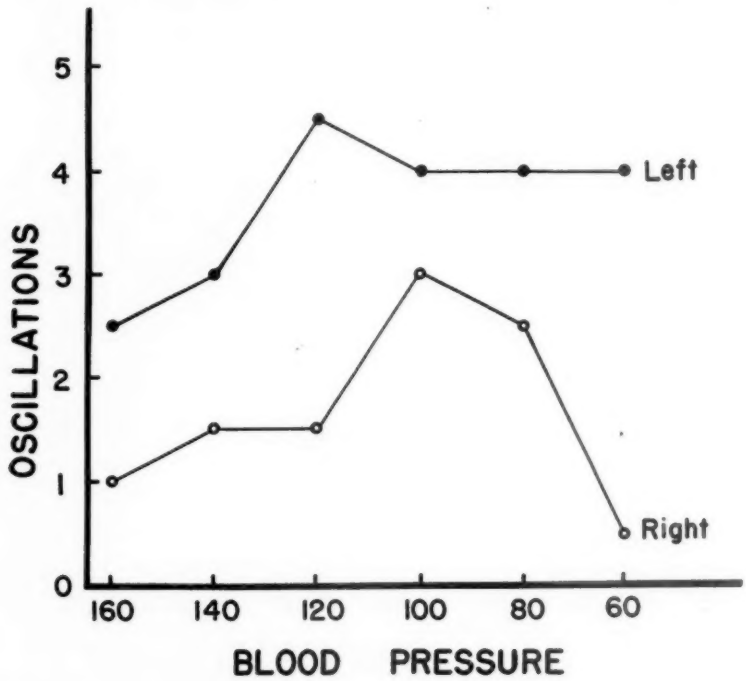


Fig. 10.—Chart showing comparison of the arterial oscillations in the normal right ankle, and in the left ankle five years after lumbar sympathectomy and popliteal aneurysmectomy, of a patient aged 71 years.

lower leg in 2 of the extremities is of sufficient volume to produce pulsations in the arteries of the feet. One of these, a man aged 73 years, seen five years following the aneurysmectomy, has had a return of palpable pulsations in the dorsalis pedis and posterior tibial arteries of the foot. The oscillations at the ankle obtained by oscillography, although not as great as in the other extremity, are of moderate amplitude (Fig. 10). The other patient, a man aged 58 years, had a return of pulsations in the posterior tibial artery at the ankle within four weeks after the aneurysmectomy and when last seen thirteen months later they were still present. The 4 patients who had intermittent claudication

when first seen were not relieved of this complaint by the removal of the aneurysm, but this symptom also was not made worse. The others at first complained of a tired feeling in the leg on exercise but did not complain of true intermittent claudication, and as the years have passed it has tended to improve.

CONCLUSIONS

1. The incidence of the arteriosclerotic type of popliteal aneurysm is increasing.

2. An arteriosclerotic popliteal aneurysm, if untreated, is a serious threat to the viability of the extremity and also to the life of the patient.

3. A two-stage method of surgical treatment is recommended, consisting of a preliminary lumbar sympathetic ganglionectomy followed approximately in ten days by an aneurysmectomy.

4. Fourteen patients with arteriosclerotic popliteal aneurysms, the ages of whom ranged from 49 to 79 years, are reported. Thirteen, or 93 per cent, survived and their extremities were saved utilizing this method of treatment. One patient died from postoperative hemorrhage and coronary thrombosis following the sympathectomy, a mortality rate of 7 per cent.

The author wishes to thank Dr. Claude E. Welch for permission to include in this group his case, a woman aged 79 years; the other 13 patients, were operated upon by the author.

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COMPLICATIONS RESULTING FROM INJURIES TO MAJOR ARTERIES

LOUIS G. HERRMANN, M.D., AND JOSEPH A. BUCHMAN, M.D., CINCINNATI, OHIO

(From the Department of Surgery of the College of Medicine, University of Cincinnati and the Cincinnati General Hospital)

MANY of the complications which follow in the wake of trauma to, or in the vicinity of, large arteries may come on so insidiously that the surgeon does not give proper consideration to his patient's apparently minor complaints. An untold number of extremities are sacrificed because the effects of the arterial insufficiency are not recognized until after extensive damage to the muscles has already taken place. We are convinced that many limbs and even many lives could be saved each year if all surgeons were more alert to the early signs and symptoms of these complications. Prompt diagnosis of the kind and site of the arterial injury with as little delay as possible in instituting definitive treatment should be the goal of every surgeon. Constant observation of all patients with suspected arterial injuries and the immediate correction of any secondary vasospasm which may become apparent are factors of paramount importance to the success of this type of vascular surgery.

It is our purpose in this presentation to emphasize the more common complications and to illustrate the late effects of such arterial injuries by a few selected case histories.

SECONDARY ARTERIAL SPASM

The most common complication of injuries to, or near, large arteries is spasm involving some part of the artery or the entire arterial bed. Extensive arterial spasm may be brought about by a variety of injuries due to violence or to surgical operations. Sometimes there is evidence of direct trauma to the arterial wall, but even more often the artery itself may be unharmed. Large arteries such as the brachial or femoral artery exhibit this phenomenon partly because of their length and exposed positions. Spasm in the artery as well as in the arterial bed is usually due to abnormal nervous reflexes since arterial thrombosis is not a common finding in the early stages of this syndrome. Intense spasm of the arteries and arterioles may last for hours or even days. The degree of arterial insufficiency which results from this superimposed vasospasm may be sufficient to bring about serious changes in the soft tissues. Peripheral arterial spasm is most severe following gunshot or crushing wounds of the extremity but may also occur after simple puncture wounds, operative procedures upon large blood vessels, or injuries to large nerves. Most students of these problems agree that prolonged arterial spasm can bring about changes in the skin, nerves, muscles, and joints of an extremity. The condition may show a tendency to disappear spontaneously but in most patients it persists sufficiently long to endanger the viability of the soft tissues. The simplest means of over-

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coming this peripheral vasoconstriction in injured extremities is by repeated novocainization of the regional sympathetic ganglia of the affected extremity.

INTRAVASCULAR INJURIES TO LARGE ARTERIES

The injection of an insoluble preparation into any major artery may give rise to serious complications. Preparations of bismuth have been injected accidentally into the gluteal artery causing intolerable pain and local areas of necrosis of the soft tissues of the buttocks. Foreign bodies are occasionally transported by large arteries and become lodged in smaller peripheral arteries.

The most frequent cause of intravascular injury is the lodgment of a blood clot which has been carried from the heart or aorta into some peripheral artery. The sudden irritation of the intima of the peripheral artery provokes marked reflex vasoconstriction in the entire vascular bed of the extremity. The stagnation of blood brought about by this vasoconstriction favors progressive arterial thrombosis.

We believe that acute arterial occlusion should be considered a real emergency and every method of promoting adequate circulation through the collateral arterial pathways should be instituted as soon as possible after the accident. If these measures fail to bring about a satisfactory re-establishment of the arterial circulation within one to four hours, removal of the embolus by arteriotomy should then be performed. Heparinization of the patient immediately after the operation insures against the re-formation of blood clots at the site of the arteriotomy wound.

EXTRAVASCULAR INJURIES TO LARGE ARTERIES

The importance of controlling hemorrhage from accidental or operative wounds of major arteries is of great concern to the surgeon not only because of the immediate loss of blood which may take place, but also because an ample supply of blood to the parts beyond the point of injury must be maintained or serious complications are certain to follow.

Knowledge of the behavior of the peripheral circulation in the extremities or in the brain after the main nutrient artery to that part has been occluded is of paramount importance. It is the duty of every surgeon who deals with vascular disorders to ascertain what alterations in the efficiency of the peripheral circulation will take place if the major arterial trunk of that part is damaged or otherwise interfered with during any surgical operation.

Primary Hemorrhage.—If bleeding is external it should be controlled as quickly as possible. Catching the bleeding point with a hemostat is acceptable except in those cases in which it is desirable to restore the function of the artery. The use of gelatin sponges as advocated by Jenkins and Janda[1] is valuable for controlling hemorrhage from wounds in large blood vessels. If the acute hemorrhage is not readily controllable by direct pressure over the bleeding point the surgeon may resort to the use of indirect pressure, that is, compression of the main trunk of the artery from which the bleeding artery arises. With vertical elevation of the extremity and mild direct pressure in the wound, bleeding from almost any peripheral artery can be controlled until preparations for permanent hemostasis can be made. In most instances it is

wise to attempt to restore the continuity of the divided artery, even though this restoration may be successful for only a few days. This is particularly true in the cases of serious hemorrhage from a severed major artery such as the popliteal artery, the femoral artery in Hunter's canal, or the common carotid artery, when they are associated with extensive extravasation of blood into the surrounding tissues.

Internal Hemorrhage.—In general, if the bleeding is not endangering the life of the patient, or if the pressure of the extravasated or accumulated blood is not seriously affecting any vital function, damaging any hollow viscus, or causing marked ischemia in the affected extremity, there is no need for immediate surgical intervention. A hematoma which continues to enlarge, and through pressure on small collateral arteries actually impairs the arterial circulation to the extent of producing impending gangrene, should be treated surgically without delay.

Secondary Hemorrhage, either internal or external, is rarely a complication of injury to a large artery even though the artery shows evidence of severe arteriosclerosis. If hemorrhage does occur under such conditions it should be treated as though it were primary. Most often secondary hemorrhage is the result of infection in the wound. In spite of the infection the bleeding vessel should be isolated and ligated with nonabsorbable material. No attempt should be made to cover the vessel and the wound should be left open and loosely packed with fine mesh gauze moistened with normal saline solution. When there is clinical evidence of a growing tumor at the site of the injury, or more pain radiating along the course of the artery, one must suspect secondary hemorrhage. Massive bleeding into some cavity of the body may result in sudden death. Surgical exploration of the wound with definite and prompt arrest of the hemorrhage by ligation of the artery without regard to the effect upon the peripheral tissues should then be done. Packing with gauze and the application of compression bandages are of little practical value in such instances for the secondary hemorrhage will most certainly recur unless the bleeding vessels are permanently occluded by ligatures.

Secondary hemorrhage may also result from erosion of major arteries. Bone fragments or bone plates and screws used in the repair of fractures may lie in contact with some major artery and the constant pulsation of the artery against the solid object may cause erosion of the arterial wall with extensive internal hemorrhage. The following case will illustrate this kind of complication.

CASE 1.—The patient, a 42-year-old white man, was referred to us on June 5, 1943. On April 26, 1943, he had been struck by the cowcatcher of a train and sustained a supracondylar fracture of the right femur. At another hospital the reduction could not be held sufficiently well with a plaster of Paris cast, so screws were placed in an anteroposterior direction to hold the fragment in position. Within twenty-four hours the right foot became cold and pulseless and he began to complain of severe pain. Loss of sensation and ability to move the toes and ankle together with a purplish discoloration soon followed (Fig. 1, *B*). Internal hemorrhage from rupture of an artery was suspected and the patient was transferred to the University Hospital. Amputation of the leg had to be performed and at operation it was found that one of the screws came in direct contact with the popliteal artery and this had resulted in the erosion and rupture of the wall of the artery (Fig. 1, *A*).

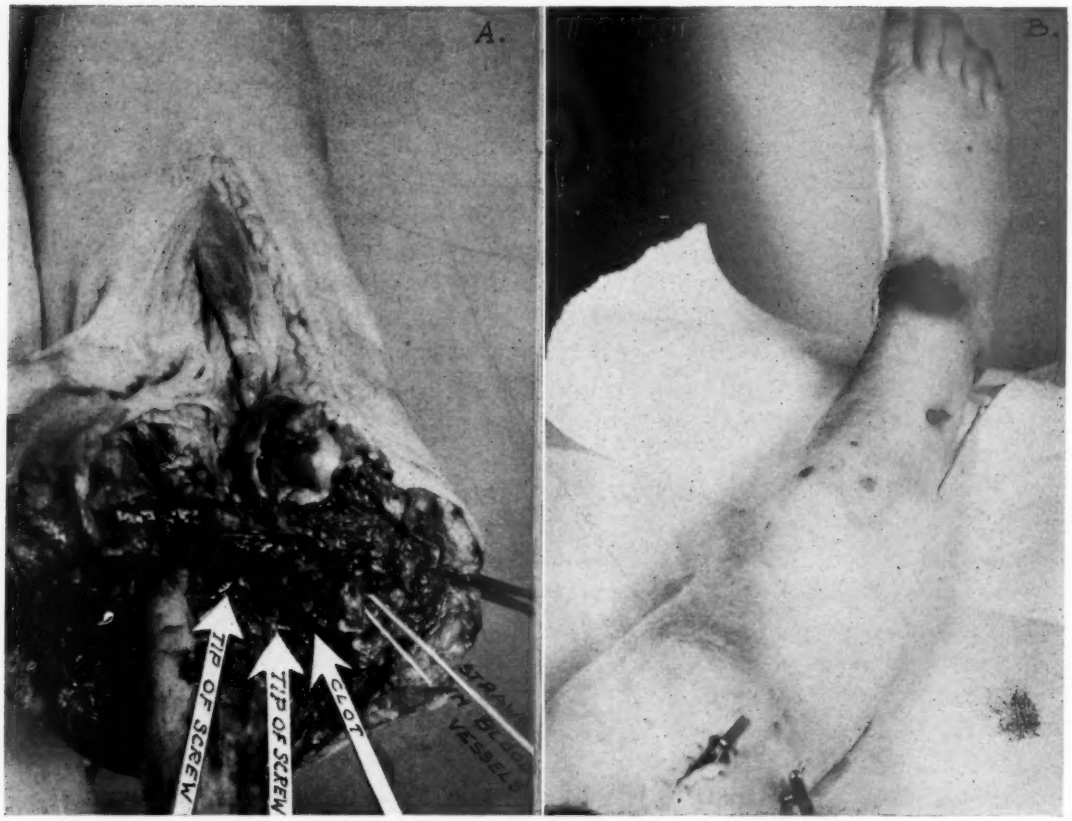

Fig. 1.—Rupture of popliteal artery by a bone screw. *A*, Note tips of screws extending through shaft of femur into popliteal space. Small arrow points to eroded popliteal artery. *B*, Position of bone screws in relation to the knee. Note mummification of the toes and gangrene of the skin on dorsum of ankle.

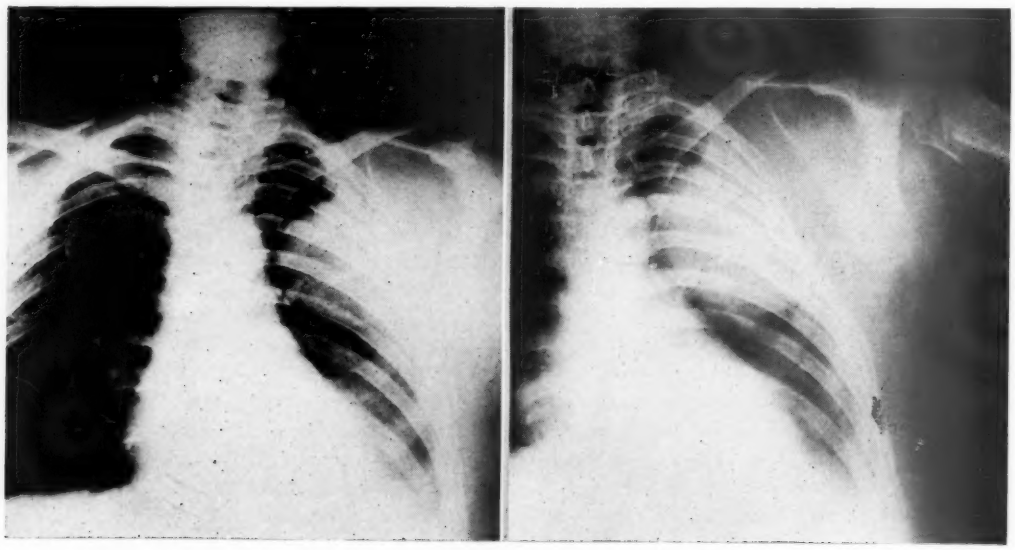

Fig. 2.—Dissecting aneurysm of the subclavian artery. Steinmann pins used to immobilize head of humerus to facilitate reduction of the fracture were inserted too far. The subclavian artery was injured. Note erosion of ribs by the dissecting aneurysm.

When a large artery is ruptured by violence its concomitant vein is usually injured also, consequently if the individual survives and if the ruptured vessels are not repaired or occluded, an arteriovenous fistula may become established. If only the major artery is injured and this artery is covered by a layer of heavy fascia, a hematoma is rapidly formed beneath this aponeurosis. Bleeding into this area will continue until the pressure within the hematoma is equal to the arterial pressure.

If the hematoma is not decompressed by surgical operation it may become so tense that the pressure will block the collateral arterial pathways and gangrene of some distal portions of the extremity will ensue. If the pressure on the collateral arterial pathways is not too great to cause gangrene, however, the mass of extravasated blood will become organized at the periphery while the center of the mass remains liquid. The mass then develops expansile pulsation. This pulsating hematoma comes to resemble a true arterial aneurysm with the characteristic systolic bruit and thrill, in contrast to the arteriovenous aneurysm in which these signs are accentuated in the systolic phase of the heart action but are also continued through diastole.

Dissecting hematomas or aneurysms may cause pressure upon nerves and give rise to severe pain or motor paralysis. They may even erode bony structures like the ribs and result in fatal hemorrhage into large body cavities. This type of complication is illustrated by the following case history.

CASE 2.—The patient was a 48-year-old white housewife who fell down three steps and sustained a fracture of the proximal end of the left humerus on Feb. 9, 1946. She was taken to a local hospital and a cast applied but the reduction was unsatisfactory.- Consequently, four days later Steinmann pins were inserted in an attempt to fix the proximal fragment and help reduce the fracture. She was discharged from the hospital one week later. Convalescence was normal for the first three weeks, but then she began to complain of burning pain in the left shoulder and left upper chest. The pain became more severe and three weeks later she coughed up some blood-tinged sputum. One week after this episode she had the first gross hemoptysis. Physical examination at that time revealed the typical signs of a dissecting aneurysm of the subclavian artery (Fig. 2, *A*). This continued to increase in size and finally ruptured into the left pleural space causing immediate death (Fig. 2, *B*).

Arterial Thrombosis.—When a major artery is merely contused and the coats of the artery are not ruptured, the damage to the intima may be sufficient to cause local intravascular clotting of the blood. If this clotting of blood is progressive it may quickly reduce the efficiency of the collateral arterial circulation by actual extension into the collateral arteries. The immediate use of heparin will effectively control the progression of the intravascular clot but it will not affect the thrombosis which has already taken place.

Leriche[2] believed that a thrombosed artery is actually a diseased sympathetic nerve and the extirpation of the thrombosed part by arteriectomy removes the factor which is irritating the sympathetic nerves and thus overcomes the reflex vasoconstriction distal to the site of thrombosis. Practical experience has substantiated this concept.

We[3] have found that it is important to use removable aluminum bands when it is necessary to occlude completely the common carotid artery. Such

bands may be removed if the patient shows signs of cerebral ischemia during the immediate postoperative period, and no permanent damage of the common carotid artery will result. An illustrative case of progressive arterial thrombosis is as follows.

CASE 3.—The patient was a 65-year-old white woman who was admitted to the hospital with an eight-day history of severe pain in the left eye, left side of the forehead, and left occipital region. For two days she had been unable to raise the left upper eyelid. On physical examination she was found to have a mild arterial hypertension and a third cranial nerve palsy. An arteriogram revealed an aneurysm of the internal carotid artery just before the bifurcation into the anterior and middle cerebral arteries. That same day, at operation under local anesthesia, the internal and external carotid arteries were occluded simultaneously for thirty minutes with no untoward effect. The common carotid artery and external carotid artery were then ligated with umbilical tape. The immediate postoperative condition was good, but within three hours signs of cerebral ischemia became apparent. The common carotid artery had been permanently occluded by a ligature so that removal of the ligature at that time would not have restored the arterial continuity. At autopsy progressive thrombosis originating at the site of the ligature and extending into the branches of the circle of Willis was found. If a removable aluminum band had been used this complication might have been avoided.

Arterial Aneurysms.—The development of an aneurysm following injury to large arteries may take various forms. This depends on whether a segment of the arterial wall gives way or whether some small spot in the wall weakens. The diffuse weakening of the wall gives rise to the *fusiform aneurysm* while a weakening of one spot in an artery causes the formation of a *saccular aneurysm.* The fusiform aneurysm may rupture at one place and assume the physical appearance of a saccular aneurysm. Such physical alterations must be kept in mind by the surgeon who plans the operative procedure for the cure of an arterial aneurysm.

The speed with which arterial aneurysms develop depends upon the extent of the damage to the outer coats of the artery. Penetrating wounds of arteries by sharp objects may cause the rapid development of a pulsating hematoma which quickly assumes the characteristics of a saccular aneurysm and should be treated as one. An illustration of such a complication to an arterial injury is presented by the following case history.

CASE 4.—The patient was a 16-year-old white boy who had received a small laceration on the flexor surface of the right forearm, in an automobile accident. The skin was sutured by a local physician and the wound healed by first intention. However, two weeks later the patient noticed a small pulsating swelling at the site of the injury. The mass continued to increase in size and at operation a saccular aneurysm of the right radial artery was excised. The efficiency of the arterial circulation in the hand remained normal in spite of the ligation of the proximal and distal ends of the radial artery.

Saccular aneurysms may remain relatively small for many years after the original injury and then suddenly, because of further trauma or some abnormal strain, start to enlarge rapidly and produce symptoms due to pressure upon surrounding structures.

Arteriovenous Aneurysms.—The complication of arteriovenous aneurysms usually occurs when a major artery and its concomitant vein are injured simultaneously. They may also result from improper handling of major blood vessels

during surgical operations. When a major artery and its concomitant vein must be ligated, as would be necessary in performing an amputation of an extremity, it is extremely important to ligate them separately.

When the ligature includes both the artery and vein, an abnormal arteriovenous fistula may develop as the vessel walls beneath the ligature undergo the usual process of necrosis and replacement with fibrous tissue. The development of such an abnormal arteriovenous communication in an amputation stump frequently results in serious cardiac complications.

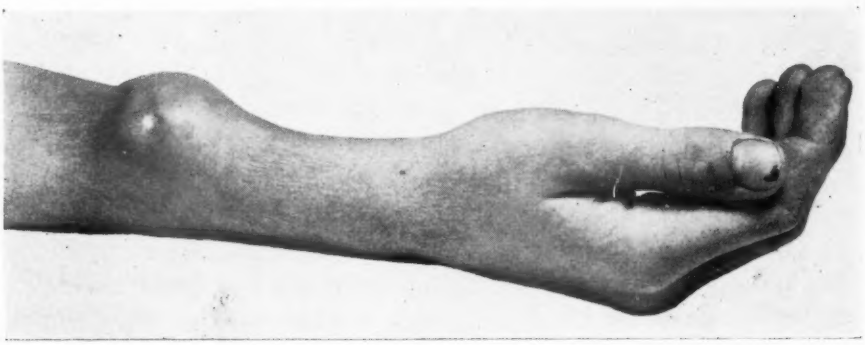

Fig. 3.—Saccular aneurysm of the radial artery following puncture wound of the forearm. Aneurysm cured by complete excision with ligation of proximal and distal ends of the radial artery.

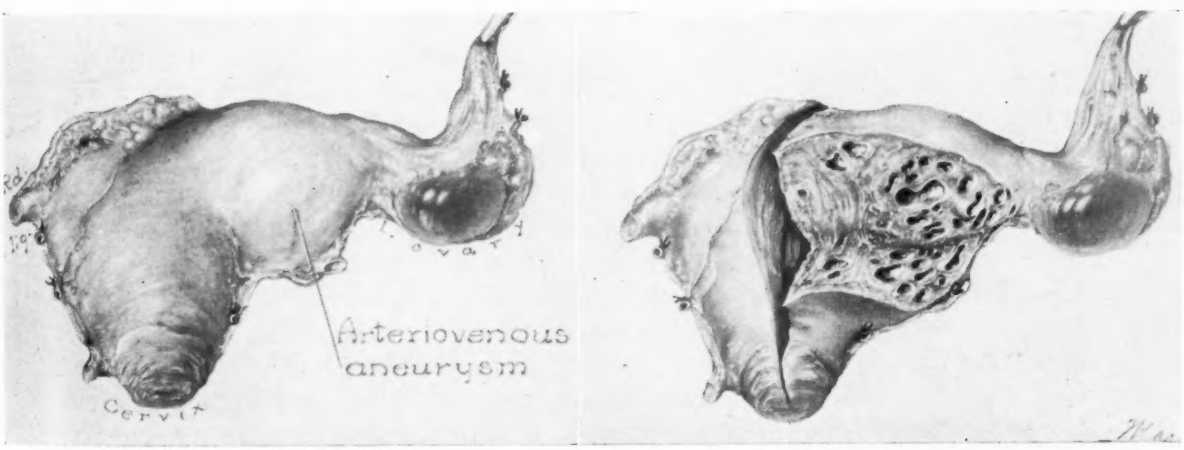

Fig. 4.—Arteriovenous aneurysm in the broad ligament of the uterus. This resulted from injury to artery and vein during an operation twelve years previously. The aneurysm was cured by supravaginal hysterectomy.

The accidental injury of the ovarian artery and vein or the uterine artery and vein by a needle or a suture during surgical operations in the pelvis may give rise to arteriovenous aneurysms in the broad ligament. The following case history illustrates this type of complication.

CASE 5.—The patient, a 38-year-old white woman, was admitted to the hospital on May 27, 1945. Twelve years prior to this admission she had had an incomplete hysterectomy, bilateral salpingectomy, and right oophorectomy. Ever since that operation she had had pain in the left lower quadrant of the abdomen. In 1938 she had a laparotomy with the freeing of adhesions which afforded no relief. The pain was described as a steady dull

ache, was becoming more and more severe, and had spread into the left flank. The classical clinical signs and symptoms of an abnormal arteriovenous communication in the pelvis were present. At operation an arteriovenous aneurysm in the left broad ligament was found (Fig. 4).

In general, any operation which does not actually close the arteriovenous fistula must be considered undesirable; and when such operations are performed there is danger of not only failing to cure the aneurysm but of causing serious circulatory disturbances distal to the arteriovenous fistula. Gangrene may develop as a result of ligation of the artery proximal to the arteriovenous aneurysm because the shunt or spillway remains open and there is no longer enough arterial force to push the blood beyond the fistula.

The most insidious and perhaps the most serious of the complications which may follow the establishment of arteriovenous fistulas following trauma to large blood vessels is the marked hypertrophy and dilatation of the heart with subsequent myocardial failure. These changes are usually late effects but cardiac decompensation has been observed within five days after the establishment of the arteriovenous communication.[4] It must, therefore, be borne in mind that it may be necessary to subject the patient to operation much earlier than ordinarily would be the case because of this cardiac complication. One method of temporarily relieving the strain on the heart under such conditions consists in ligation of the *vein* some distance *proximal* to the arteriovenous communication.

SUMMARY

We have presented a review of some of the complications which may follow various types of injuries to major arteries and their concomitant veins. We believe that a thorough understanding of such complications will enable surgeons to reduce the number of catastrophies which all too frequently nullify their most conscientious efforts. Lord and Breidenbach[5] have emphasized the importance of having the operating room of every hospital properly equipped to care for all types of injuries to the major arteries and they suggest that properly trained surgeons should be available at all times to handle such injuries. We[6] agree that a determined effort should be made to teach young surgeons the important factors in the management of injuries to large blood vessels and then they should be provided with facilities which will permit proper care of such injuries. The progress of this important field of surgery will depend greatly upon the success and the thoroughness of such an educational program.

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THE CORTICOADRENAL FACTOR IN HYPERTENSION

GEZA DE TAKATS, M.D., CHICAGO, ILL.

(From the Department of Surgery, University of Illinois, College of Medicine, and St. Luke's Hospital)

INTRODUCTION

THERE are several reasons why an investigation of the corticoadrenal function in human essential hypertension seems of interest. They can be briefly summarized as follows:

1. Experimental renal hypertension produced by the Goldblatt clamp is greatly diminished or disappears after bilateral adrenalectomy in dogs whose life is maintained by cortical extracts.[1, 2, 3, 4] Whether this is due to a specific action of the cortex on renal hypertension or due to the general changes produced by adrenalectomy is uncertain, but it seems that in adrenal insufficiency there is a reduction of sensitivity to the pressor effect of renin.[5, 6, 7, 8] This has been explained by the fall in concentration of hypertensinogen in the blood,[4, 9] which returns to normal on administration of cortical extracts or desoxycorticosterone.

2. According to the concept of Selye,[10] hypertension is an expression of the "general adaptation syndrome." In his animal experiments corticoadrenal stress as manifested by storage and elimination of cortical lipids and decrease in the lymphocytes in the blood is an essential part of the "alarm reaction."[11, 12]

3. Epinephrine infusion or splanchnic nerve stimulation may cause increased corticoadrenal secretion; splanchnic nerve section, however, does not interfere with the basic corticoadrenal output.[13] This effect is demonstrated by the decrease of the cholesterol and ascorbic acid content of the gland, but mediated through anterior pituitary action.[14]

4. In man, some authors believe that the incidence of hyperplasia or adenomatous change in the adrenal glands of hypertensives is higher than in the control group[15, 16]; this is denied by others.[17, 18]

5. The full-blown Cushing's syndrome shows a plasma electrolyte disturbance which is diametrically opposed to that seen in Addison's disease.[19, 20] Experimentally, the overactivity of the eosinophil cells of the anterior pituitary gland, which are trophic to adrenal cortex, produce diastolic hypertension no matter how this eosinophil preponderance is produced.[21]

6. In a hypertensive patient a subsequently developing Addison's disease produced a normal blood pressure, as long as the patient was kept on salt alone; when desoxycorticosterone was administered the elevation of blood pressure returned.[22] When normal individuals are subjected to a sudden withdrawal of sodium, they lose water, weight, and go into a syndrome characterized by increased sweating, insomnia, and extreme weakness[23]; but in essential hypertension this does not happen. The patients lose minimal weight

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and are asymptomatic. This may be due to renal changes or the changes in the kidney mediated by adrenal cortex.[24] The low sodium diet or the low protein rice diet may well act through the adrenal cortex.[25] Desoxycorticosterone acetate when administered intravenously acts as a pressor substance in hypertensive individuals.[26]

In previous reports from this clinic[27, 28] it was pointed out that a small group of juvenile or middle-aged hypertensive patients exist who in spite of favorable preoperative studies fail to show a favorable response to the operation; others show a delayed response, appearing as late as six months after operation.[29] For this reason it was decided to study a group of hypertensive patients in regard to their corticoadrenal function.

METHOD OF STUDY

It must be stated immediately with regret that hormonal studies were not within the scope of the laboratory. As a matter of fact, the sex hormone production is said to be diminished in hypertension[17] and during the general adaptation syndrome the sex hormone production is not stimulated at the expense of sugar active and salt active corticoids.[10]

The "11 oxysteroids," which increase sevenfold on the administration of adrenocorticotropic hormone,[30] were not studied. Our methods were so selected that first a simple test was determined for purposes of orientation and when this was found to be positive, other methods were used to corroborate the suspicion that adrenocortical hyperfunction might be present.

The Insulin Tolerance.—In 1934 Fenn, Trump and I[31] described a test for insulin sensitivity and summarized the previous literature. Our aim was to distinguish an insulin-resistant from an insulin-sensitive diabetic patient. A group of factors was listed which were known to increase the action of insulin, such as thyroidectomy, hypophysectomy, pancreatectomy, high carbohydrate diet, and alkaline diet. To these our animal experiments added celiac ganglionectomy, adrenal denervation, and splanchnic nerve section.[32, 33] One factor which has since then become known mostly through the work of Jensen and Grattan[34] is the glycotropic, anti-insulin substance of the anterior pituitary gland which requires the presence and functional activity of the adrenal cortex. Heinbecker and Rolf[35] showed that the anti-insulin factor resides in the eosinophil cells of the anterior pituitary gland. It is likely that many of the factors listed in our previous publication act through this mechanism.

Our original test called for an injection of 0.01 unit of insulin per kilogram of body weight, given intravenously, but since most workers adopted a tenfold dose and since insulin resistance is thus more strikingly demonstrable, a dose of 0.1 unit of insulin per kilogram of body weight was used in our present studies.

The test at present consists of the determination of a fasting blood sugar, after which insulin is injected intravenously. Blood sugars are determined one-half, one, two, and three hours after the injection. A graph illustrates

some of the typical responses to this dose of insulin in hypertensive individuals (Fig. 1). It will be noted that some curves showed a good response at thirty minutes, with rapid recovery of the blood sugar level in one to two hours; another curve shows a delayed response which does not appear until one hour after injection, and one curve shows a complete resistance to this dose of insulin. Curves may also show a normal dip but a failure of normal return to the fasting level of blood sugar. A recent refinement of insulin

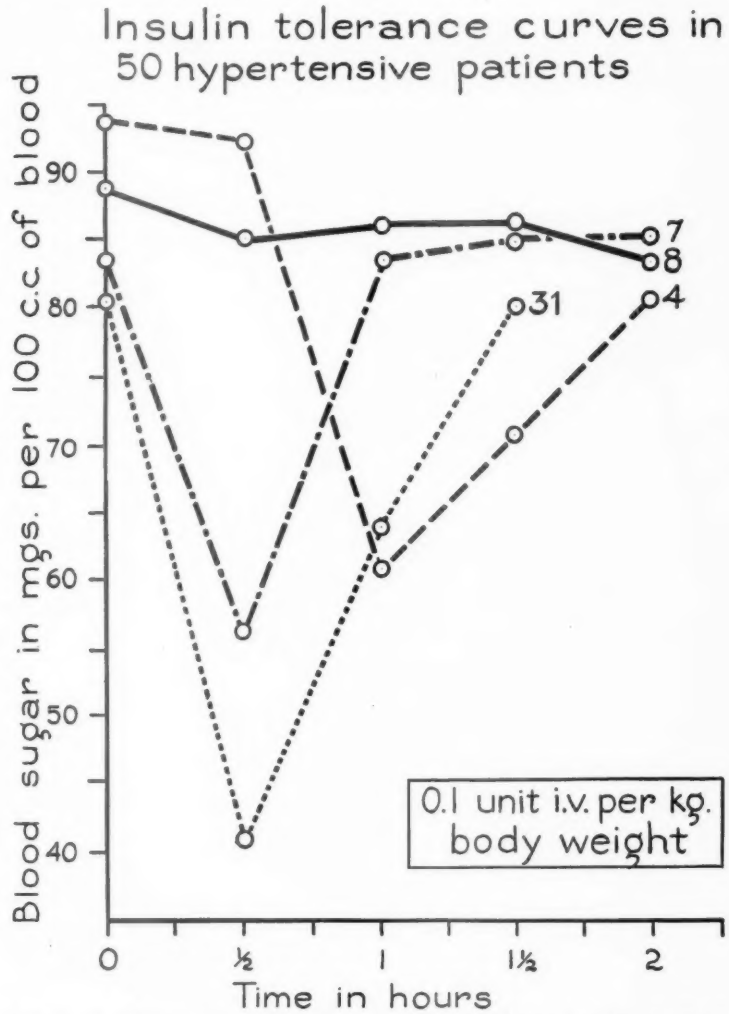

Fig. 1.—Insulin tolerance curves on fifty consecutive hypertensive patients. Note that thirty-one show a normal response, four show a delayed response, and eight show no response at all.

tolerance[36] test studies the rate of fall in reducing substances in taking samples at short intervals, especially at ten and twenty minutes. A delay in the fall was observed in malignant hypertension and acromegaly.

Insulin tolerance curves were determined on 50 consecutive hypertensive patients during their preoperative study. Of these, 31 showed a normal response, 4 showed a delayed response, 7 showed an early dip and returned

faster than usual to normal, and 8 showed no response at all. Obviously, another possible curve exists, namely, a poor response to the insulin hypoglycemia by failing to rise from the initial dip.[37] Such curves are seen in Simmonds' pituitary cachexia and in Addison's disease. Interestingly enough, patients who show a great deal of fatigue and listlessness after operation may present such a slow rise following the hypoglycemic dip. Their convalescence may be greatly hastened by cortical extract.

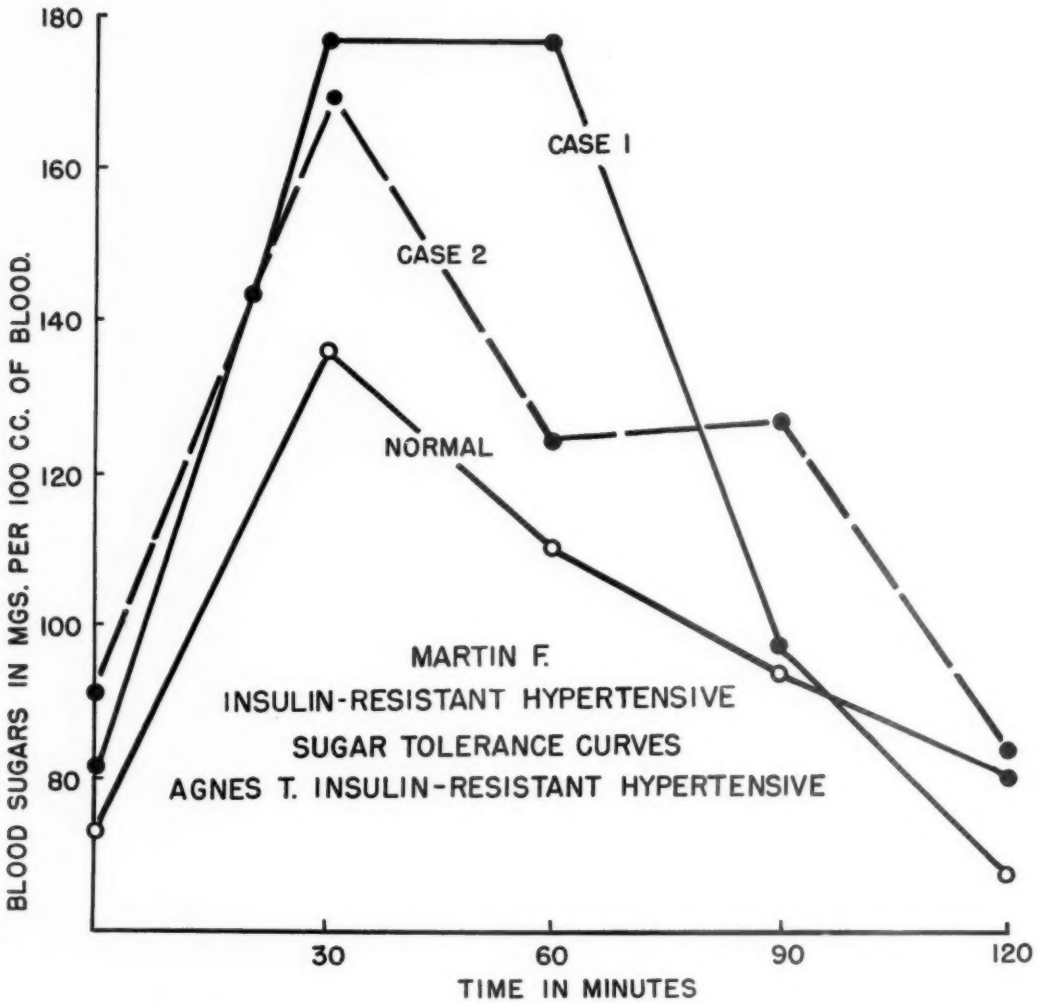

Fig. 2.—Intravenous sugar tolerance curves. Graph illustrates a normal sugar tolerance curve, determined according to the method of Soskin.[38] Two other curves illustrate sugar tolerance curves of two patients (Case 1 and Case 3), both of which show insulin resistance.

The eight patients exhibiting insulin resistance were of particular interest. If their insulin resistance was really due to an increased pituitary corticoadrenal activity, what other tests could be used to confirm this assumption and what was their postoperative course? The following additional tests were done in the insulin-resistant group of hypertensive patients:

The Intravenous Sugar Tolerance (Soskin[38]).—Fuller Albright and his co-wokers[37] stated that the "sugar hormone" of the adrenal cortex is responsible for the corticoadrenal symptoms of the Cushing's syndrome. For this reason, in patients who were suspected of corticoadrenal stress, a sugar tolerance curve was obtained. But since the tests were to be repeated after operation and since splanchnic nerve section accelerates upper gastrointestinal motility, it was felt that the intravenous route would eliminate the different rates of absorption from the gastrointestinal tract. The patients were

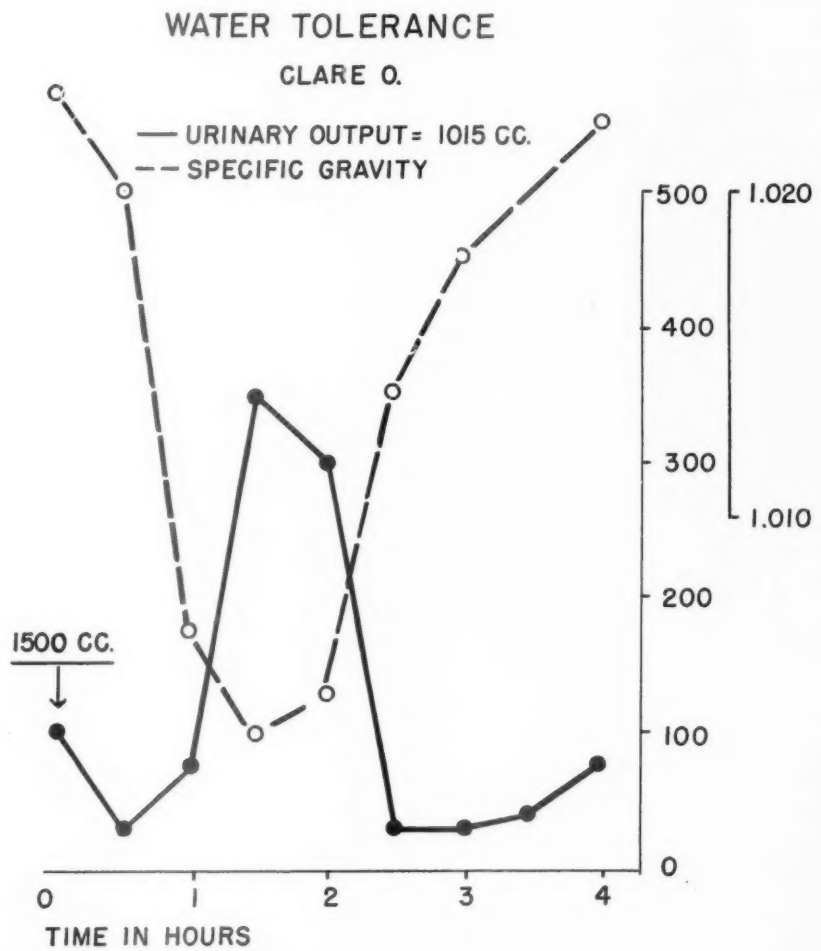

Fig. 3.—Water tolerance of a normal individual.

given ⅓ Gm. of dextrose per kilogram of body weight intravenously in 50 per cent solution. Blood sugars were determined before, 30, 60 and 120 minutes after the injection. A normal curve is shown in Fig. 2, together with two abnormal curves (Case 3). Case 2 showed a complete insulin resistance prior to operation. Three months later the insulin resistance diminished and the patient was sugar-free on a liberal diet without insulin.

Desoxycorticosterone acetate which has a definite pressor effect in hypertensive patients[26] showed no effect on the intravenous sugar tolerance. It

is obvious that this synthesized product is by no means equivalent to the full activity of the adrenal cortex; besides, the salt hormone should not affect sugar tolerance.

The Water Tolerance.—Fasting subjects were given 1,500 c.c. of water to drink in twenty to thirty minutes, after being deprived of water and food for fourteen hours. The bladder is emptied just before and every thirty minutes after the ingestion of water for four hours. Volume and specific gravity are determined in the individual specimen.

This is essentially the second half of the well-known concentration-dilution test except that the volume and specific gravity are followed in half-hour samples. Normal subjects eliminate 1,200 to 1,500 c.c. of urine; the specific gravity fluctuates inversely with the output (Fig. 3).

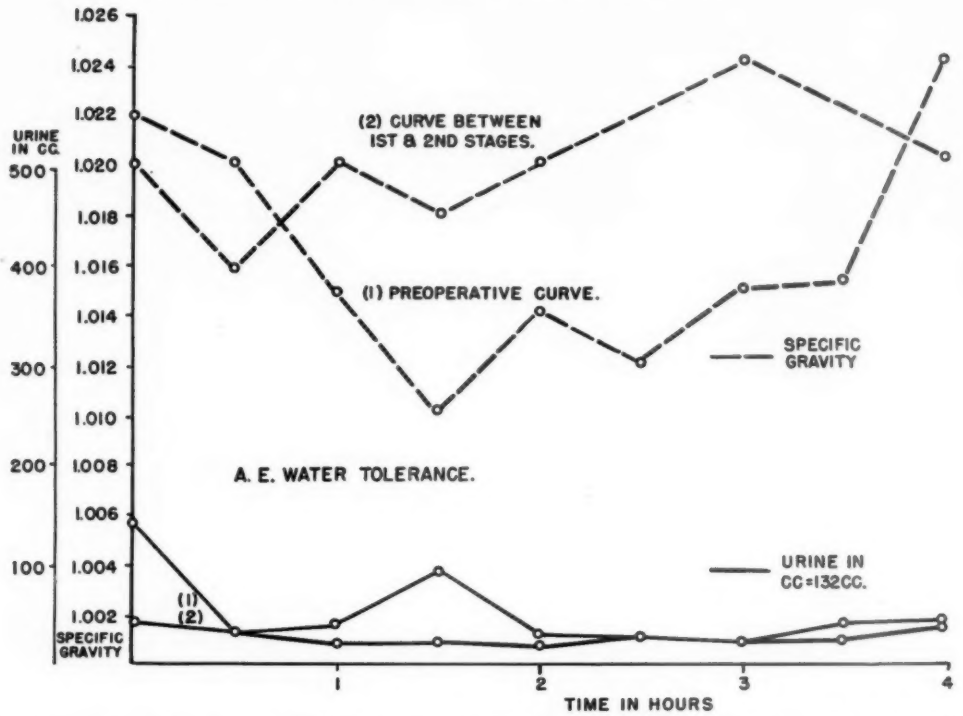

Fig. 4.—Water tolerance of patient (Case 3) with a cortical adenoma proved at operation. Note fixed high levels of specific gravity and low individual specimens of urine.

It was originally thought that this test would give a measure of salt and water retention and thus relate to the salt-water hormone of the adrenal cortex. Truly enough this is illustrated in one patient (Case 3, Fig. 4) who was not only partially insulin resistant but who had a large corticoadrenal adenoma removed during the second stage of splanchnic nerve section (Fig. 5). It became obvious, however, that in the average hypertensive patient without corticoadrenal involvement, this is an excellent renal function test and that patients can be readily grouped in six patterns.

In another communication[39] these patterns were described in detail; their value lies in establishing a type of renal impairment which seems un-

influenced by splanchnic nerve section and thus is significant in predicting a poor result. Whether the pattern shown in Fig. 4 is typical of corticoadrenal hyperfunction needs to be investigated.

Other Tests.—Trials were made with the salt tolerance test of Soffer[40] with the uric acid-creatinine ratio of Thorn[30] and the NaCl ratio of Selye.[41] Either they were not simple enough for our purpose or there is as yet insufficient experience to evaluate their significance.

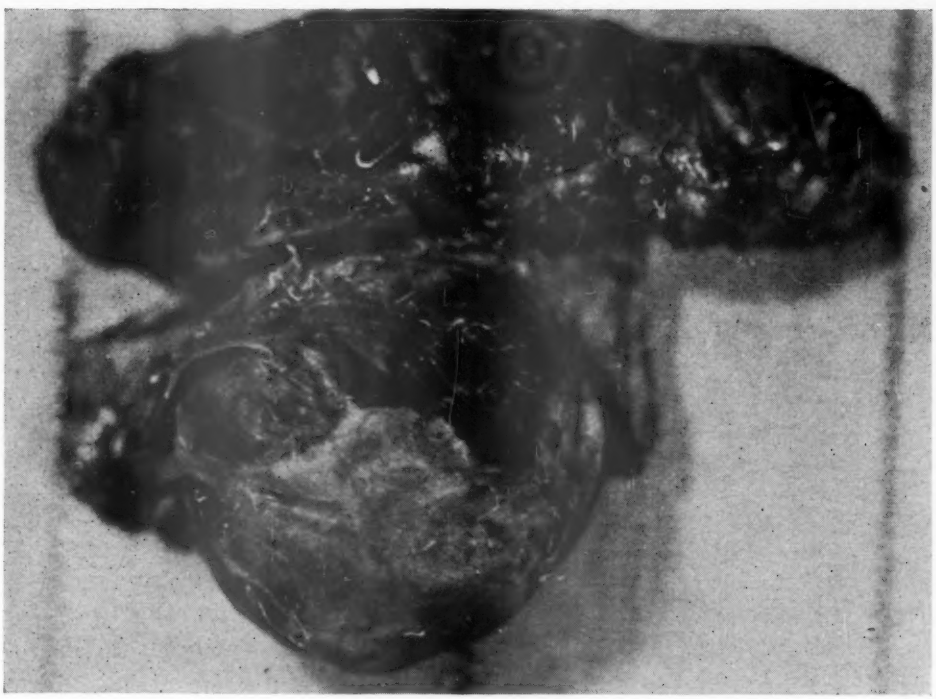

Fig. 5.—Cortical adenoma removed at operation.

DISCUSSION

In a previous paper[28] we have offered a diagram of factors which are known to affect directly or indirectly arteriolar tone. In this report the corticoadrenal factor has been studied. Limited experience with the simple clinical tests of insulin, sugar, and water tolerance would indicate that a group of patients (16 per cent in the small series of fifty) have shown corticoadrenal hyperactivity; interestingly enough, if this is due to simple hyperfunction, splanchnic nerve section, gradually over a period from three to six months, diminishes this activity. That the adrenal cortex is influenced by sympathetic activity has been suggested by some of our early histologic studies with Cuthbert[33] and recently persuasively proposed by Vogt[13] and by Long.[14] There still remains of course the hormonal action of the eosinophil cells of the anterior pituitary gland on the adrenal cortex and also the autonomous activity of a corticoadrenal adenoma.

From a practical standpoint, the use of the simple insulin tolerance is suggestive of corticoadrenal hyperfunction. In such hypertensive patients one

may find corticoadrenal adenoma or a simple hypertrophy. Whether a bilateral partial resection of the adrenal gland should be done, as advocated years ago by De Courcy,[42] or whether splanchnic nerve section per se will bring about a slow involution is yet to be determined. At any rate, we now have simple methods at our command to investigate this factor.

There has been no correlation as yet between the insulin-resistant patients and those patients who respond to sodium restriction, but it is possible that this would be a simple way to select hypertensive patients for such diet if it could be shown that sodium restriction acts through dampening the corticoadrenal factor as suggested by Grollmann and associates.[25] Also, the group of hypertensive patients who have not responded well to splanchnic nerve section and yet do not show extensive adrenal damage may well be benefited by such a procedure.

Attention should be called to the water tolerance of hypertensive patients which seems to have prognostic value as to results from the operation. It is obvious that the corticoadrenal factor, the posterior pituitary factor, which has not been discussed here, and the renal factor are all at play; however, certain curves are so suggestive of late nephrosclerosis that together with the results of other renal function tests they form a contraindication to operation.

SUMMARY

There are experimental data and clinical observations recorded in the literature which suggest that corticoadrenal activity is a factor at least in some cases of hypertension. In this preliminary study the significance of insulin tolerance, sugar tolerance, and water tolerance has been discussed. Insulin resistance means an activity of pituitary eosinophils, mediated through the adrenal cortex. The sugar tolerance in corticoadrenal stress seems to be diminished, just as in acromegaly. The water tolerance, dependent on a number of factors, is a sensitive index of renal function and has prognostic value as to the expected results from splanchnic section.

CASE REPORTS

CASE 1 (St. Lukes's Hospital, No. 94706).—A. T. was admitted to the urologic service on June 12, 1947, complaining of headaches, vertigo, and dyspnea on exertion. A diagnosis of chronic glomerulonephritis was made in a local community hospital. This 45-year-old patient had a long history of renal disease. Twenty-five years previously she had eclampsia with her first pregnancy and was unconscious for four days. The second and third pregnancies were uneventful. Eleven days after her fourth delivery, however, she suffered a cerebrovascular accident and was completely paralyzed on the right side. Since this time the patient has been aware of having hypertension, being told that it reached the 200 mm. of mercury level. One week prior to entrance the left side became numb and this prompted the patient's entrance to St. Luke's Hospital. After a urologic survey which was negative she was transferred to our service for management.

On admission the patient's blood pressure was 240/140 mm. of mercury, with a regular heart rate of 92 beats per minute. The eye grounds revealed a type II hypertensive fundus with a left-sided optic atrophy. She had been blind in the left eye since the age of thirteen years, with a sudden onset of unknown cause. The heart occupied 52 per cent of the thorax and the great vessels indicated some widening. The cardiogram revealed myocardial pathology on a hypertensive basis. T was inverted in Leads L and $6F_4$ and depressed

in II, and there was left axis deviation. Single specimens of urine revealed no pathology in elements. She was unable to concentrate above 1.013, but diluted to 1.002 specific gravity. The fifteen-minute phenolsulfonphthalein test revealed 20 per cent excretion of the dye and the urea clearance was 89.58. A water tolerance revealed that she excreted 869 c.c. of urine after ingesting 1,500 c.c. and reconcentrated the urine from an initial level of 1.019 to 1.009 at the end of four hours. The insulin tolerance revealed a completely flat curve (89, 85, 86, 86, and 84 mg. per cent). A repetition of this test revealed again this resistance to insulin (105, 94, 96, 86, and 87). The sugar tolerance ($\frac{1}{3}$ Gm. of dextrose per kilogram of body weight given intravenously) gave a fasting blood sugar of 81 mg. per cent with values of 177, 177, 97 and 67 mg. per cent at half-hour intervals. Blood chemistry was within normal limits. The blood count was normal, including 12.6 Gm. of hemoglobin per 100 c.c. of blood.

The medical consultant found moderate enlargement of the heart to the left. The reflexes were active but within physiological limits. The patient showed a fair drop of blood pressure after 9 grains of Sodium Amytal, from 190/120 to 140/100 mm. of mercury. On hyperventilation together with pressure on the carotid sinus the blood pressure was lowered to 166/104 mm. of mercury. On administration of Etamon (4.3 c.c. intravenously) the blood pressure fell from 230/120 to 126/? in one minute and returned to the original level in six minutes.

This patient was judged suitable for splanchnic nerve section. Of unusual interest was the abnormal water and insulin tolerance. For this reason the adrenals were specifically investigated at operation by completely freeing and inspecting them.

Operations.—The two stages of dorsolumbar sympathectomy were performed on June 25, 1947, and July 11, 1947. On both sides the major splanchnic nerve was removed from the midthoracic level to its entrance in the celiac ganglion and the ganglionated chain was removed from above the eighth dorsal to below the second lumbar ganglia. A biopsy was taken from the right renal cortex which showed a slight nephrosclerosis. The adrenal gland on the right seemed normal. The left adrenal, however, seemed larger than usual, somewhat firm, and nodular. Since the pressure at this stage of operation was very low and unstable, it was felt advisable not to disturb it until the failure of the bilateral sympathectomy should be demonstrated.

The patient's surgical convalescence was uneventful. Because of the preoperative findings and the possible enlargement of the left adrenal, the salt tolerance of Soffer was run in the postoperative period. Without the desoxycorticosterone acetate, the patient excreted 35 per cent of the ingested chloride ions, whereas after the drug, she excreted 5.3 per cent, indicating a normal response to the drug. On discharge the blood pressure was 160/80 mm. of mercury.

Postoperative Course.—The patient was re-examined on October 18, a little over three months following the second stage of dorsolumbar sympathectomy. The cardiogram and two-meter chest film showed definite improvement. She had lost twenty pounds and, aside from some residual soreness in the back, felt very well. She had started to do her own housework. The blood pressure, however, was 160/115 mm. of mercury, an improvement over the preoperative reading. Insulin tolerance was 91.5, 57, 72, and 81 mg. per cent, which now fell within normal limits.

Comment.—This case history indicates a type of hypertension which manifests insulin resistance or other evidence of corticoadrenal activity such as a tendency to salt and water retention and hyperproteinemia, which are suggestive of corticoadrenal hyperfunction. It is most interesting that this patient, although not showing a change in insulin response immediately after the operation, exhibited a normal insulin response three months after operation, together with a marked clinical improvement. The improvement, however, was temporary, and nine months after operation, while asymptomatic,

she returned to the hospital with blood pressure at the preoperative level. At this time, the left adrenal gland was re-explored and found to be normal and an uncut left lumbar chain was resected. This resulted in a fall of blood pressure to 160/100 mm. of mercury. The insulin and water tolerance were now within normal limits, and the sugar tolerance was now quite normal. The last examination eleven months after the operation showed the blood pressure to be varying between 180 and 174 systolic, 110 and 108 diastolic pressure. This is a good result considering the amount of organic vascular damage.

CASE 2 (St. Luke's Hospital, No. 103072).—M. F., a 41-year-old manufacturer, entered St. Luke's Hospital with a hypertension of six years' duration. In 1941 his family physician discovered diabetes and hypertension on examining him for severe headaches and weight loss. The blood pressure fluctuated a great deal and varied between 200 and 160 mm. of mercury. A year before admission severe substernal ache appeared on exercise. Treatment consisted of rest, sedatives, and nitroglycerin. He was placed on a weighed diet with 20 units of protamine zinc insulin. Later dyspnea developed on very little exertion and vision became blurred in spite of newly fitted glasses. The patient's father died of coronary occlusion at the age of 74 and his mother died of cancer at the age of 60.

On admission the patient's blood pressure was 210/136 mm. of mercury on the left arm. He showed some evidence of cardiac decompensation. The eye grounds showed marked sclerosis of the arterioles and several white dots indicating previous hemorrhage but no cotton wool exudates. The heart was slightly enlarged to the left, but its rate was regular and there were no murmurs. The cardiogram revealed sinus rhythm and left axis deviation. On the two-meter chest film the cardiothoracic ratio was 48 per cent and there was considerable vascular engorgement. The basal metabolic rate was -6 per cent. Blood chemistry revealed a blood sugar of 112 mg. per cent and a blood cholesterol of 365 mg. per cent on the preoperative diabetic management. The urea nitrogen was 16.0; nonprotein nitrogen, 40 mg. per cent. He concentrated urine to 1.025 and diluted to 1.005, the phenolsulfonphthalein test showed 40 per cent excretion in one-half hour, and the urea clearance was 52.93 c.c. per 100 c.c. of blood. Total protein was 8.12, with 2.00 albumin and 6.12 globulin.

Four insulin tolerance curves were determined, one before, one after the first stage of splanchnicectomy, and two after both stages were completed. The four curves are given in Table I.

TABLE I

1. Preoperative curve	112	89	94	91.5	90
2. After first operation	124	114	116	117	124
3. After second operation	124	102	102	110	117
4. Five months after second operation	120	73	64	81	116

Since he weighed 200 pounds, the insulin given was 9 units intravenously, which failed to produce an appreciable drop in the blood sugar levels. Vasomotor tests revealed the following: Ice water raised the blood pressure from 190/120 to 196/144 mm. of mercury. On exercise the pressure rose from 196/144 to 238/130 mm. of mercury. On Etamon the lowest pressure obtained was 160/114 mm. and on Sodium Amytal the lowest pressure obtained was 160/100 mm. of mercury.

Sympathectomy was advised for two reasons: First, to stabilize the diastolic pressure around 110 mm. of mercury if possible and, second, to improve the insulin resistance and thus perhaps the diabetes.

Operations.—Operations were done on November 7 and December 3, 1947. Both stages were followed by some atelectasis and considerable intercostal neuritis, but he left the hospital in good condition on December 17, with no digitalis or insulin, with a diet of protein 160,

fat 70, carbohydrates 90, and a blood pressure of 154/100 mm. of mercury lying down, which fell to 60/0 mm. of mercury on standing.

Postoperative Course.—For some time the patient complained of much abdominal tenderness and required narcotics. He ate poorly. A roentgenologic study of the gastrointestinal tract was negative. Gall bladder visualization revealed a well-functioning gall bladder. The blood pressure was 160/100 in bed; on standing it fell to 100/60 mm. of mercury. Two months after operation the patient for the first time showed some response to insulin. The blood pressure was 160/100 mm. of mercury and he had started working again. He showed considerable improvement and had a fasting blood sugar of 117 mg. on the preoperative diet without insulin. Five months after operation, the insulin tolerance was 120, 73, 64, 81, 116 mg. per 100 c.c. of blood. The blood pressure was 160/100 mm. of mercury lying down and 138/80 mm. on standing. The result persists to date (June 15, 1949).

CASE 3.—A. J. E., a 53-year-old production manager, was first admitted to St. Luke's Hospital on September 14, 1947. He had known of hypertension for ten years, at which time the blood pressure was 160 mm. of mercury. Five years before admission the systolic pressure was said to be 200 mm. of mercury. Three months before admission he had a right-sided apoplexy, which left him with some residual spasticity in the hand with difficulty in writing. He complained of no headaches, dizzy spells, chest pain, or edema.

On admission the blood pressure was found to be 212/130 mm. of mercury. Reflexes on the right were exaggerated. The eye grounds showed grade II retinopathy. The heart and aorta showed moderate enlargement; the cardiogram revealed myocardial pathology on a hypertensive basis. The urea nitrogen was 23.9 mg. per cent; the nonprotein nitrogen, 40 mg. per cent, giving a urea ratio of 50. Other values of blood chemistry, including sugar, cholesterol, and total protein, were within normal limits. The urine showed no pathologic elements; the water tolerance revealed a curve suggestive of cortico-adrenal activity of the salt factor (Fig. 4). The fifteen-minute phenolsulfonphthalein excretion was 25 per cent; the urea, 40.49 c.c. per 100 c.c. of blood. The intravenous pyelogram was normal. The insulin tolerance showed a diminished response starting with a fasting blood sugar of 84 mg. per cent, a maximal dip to 56 mg. per cent at half an hour, followed by blood sugars of 75, 85, and 81 mg. per cent at half-hour intervals, an abnormal curve. Basal metabolism was +1 per cent. The cold pressor test raised the blood pressure to a ceiling of 240/165 mm. of mercury, whereas the Sodium Amytal test lowered it to a minimum of 110/90 mm. of mercury. Because of the marked variability of the blood pressure and comparatively little organic damage with the exception of the cerebrovascular accident, operation was advised. The significance of the water tolerance and insulin tolerance was not fully appreciated.

Operations.—A two-stage splanchnic nerve section and lumbar dorsal sympathectomy were performed. Renal biopsy from the right side revealed nephrosclerosis and chronic interstitial inflammatory foci in the kidney. Between the two stages the water tolerance test was repeated and showed a pattern identical with the first one. The blood pressure was 228/148 mm. of mercury a month after the first stage, and the patient suffered from intercostal neuralgia. At the second stage a large cystic adenoma of the left adrenal gland was found and was removed with the adrenal gland from which it could not be separated.

Postoperative Course.—The patient's blood pressure was 150/100 on discharge. The water tolerance now showed a good dilution and reconcentration in four hours. The insulin tolerance on May 16, 1948, ten weeks after removal of the cortical adenoma and bilateral splanchnic nerve section, was 110, 78, 51, 68, and 79 mg. per cent, showing a return to normal. The blood pressure now is 170/110 with the patient lying down and 134/100 standing up.

CASE 4.—H. F., a 23-year-old housewife, was admitted to St. Luke's Hospital on May 11, 1942, complaining of nervousness for six years; severe headaches for two years; "strokes" one and two years before admission, with transient aphasia and paralysis of left and right upper extremity for four to six weeks each time; coldness of lower extremities; and occasional hematuria.

The patient was perfectly well until six years before admission, when she became very nervous. Five years before she had a severe toxemia of pregnancy with conclusions and generalized edema for the entire third trimester. The infant was stillborn. While the patient had scarlet fever at the age of 9 years, which left her with a discharging ear, she had no kidney trouble and the blood pressure was not elevated before the pregnancy. The family history was not contributory.

Fig. 6.—Intravenous pyelogram of H. F. (Case 4). Note calcified scattered spots in region of right adrenal gland. Her history together with low blood pressure and marked insulin sensitivity are highly suggestive of adrenal insufficiency.

On admission, the patient's blood pressure was 135/90 mm. of mercury. Physical examination revealed a slight left lumbar tenderness and residual weakness and spasticity of both arms and hands. There was left facial weakness. Eye grounds revealed a slight bitemporal pallor of the discs. The heart occupied 42 per cent of the thorax; electrocardiogram showed evidence of myocardial damage. She concentrated urine to 1.022 and diluted to 1.002; excreted the dye to 20 per cent in fifteen minutes. The urea clearance was 74.4 c.c. (standard). There was persistently more than 50 mg. of albumin in the urine. The intravenous pyelograms were normal, but there were some calcified spots to the right and left of the midline suggestive of calcification in the suprarenal glands (Fig. 6). There was some old infiltration in the upper portion of the right lung which appeared to be well organized. Sodium Amytal depressed the blood pressure from 130/94 to 100/80 mm. of mercury. On immersion into ice water the pressure rose from 135/90 to 140/96; epinephrine raised the blood pressure from 130/90 to 190/100 mm. of mercury. The impression was that of a post-

eclamptic hypertension resulting in diffuse arteriolar disease. The diastolic pressure was consistently above 90 mm. of mercury, but the systolic was low due to myocardial damage or possibly damage to the adrenal glands.

Operations.—Operations were performed on May 20, 1942, and June 8, 1942. Following the first stage the patient exhibited a temperature of 104.6° F., a slow pulse and respiration, and a marked mottled peripheral cyanosis. This was thought to be a cerebral vascular accident in the midbrain or a Waterhouse-Friedrichsen syndrome which fortunately subsided in three days. The second stage was performed nineteen days after the first one without any unusual complication. The kidneys were small and firm and both adrenals were also visualized; while the adrenals felt smaller and more nodular than normal, there was no evidence of tumor or calcification on palpation. The renal biopsy taken from the right kidney showed marked fibroblastic changes; there were wedgelike sections of cellular fibrous tissue which extended deep into the parenchyma. Here the tubules and glomeruli had undergone marked retrogressive changes. There were clusters of atrophic glomeruli reduced to masses of hyaline material and the tubules had disappeared almost completely. There were also lymphocytes with small residues of tubule cells. There were various stages of involution but outside these wedges the tubules contained columnar lining cells and the lumina were filled with granular precipitates. The glomerular tufts in these portions were also cellular and had considerable fibrous stroma. The large blood vessels included in the scarred portions had very narrow lumina and intimal fibrous tissue thickenings, but the blood vessels elsewhere also had thick muscular walls with some fibrous thickening along the intimal edge. The interpretation of these findings was that nephrosclerosis was the main tissue change.

Postoperative Course.—When the patient left the hospital on August 19, 1942, the blood pressure was 112/86. The epinephrine sensitivity decreased. She was re-examined on July 3, 1943, and found to have a blood pressure of 110/70 lying down and 100/70 in the standing position. She felt well and used the paralyzed arm more freely. Seven years later she still has a normal blood pressure but is adynamic.

Comment.—This was a frail, constitutionally inferior patient who received a severe vascular lesion during pregnancy. Whether there was a latent adrenal insufficiency present was uncertain and it was not feasible to test her for this at the time. The cerebral, cardiac, and renal lesion might have been embolic in nature, originating from a subacute bacterial endocarditis, but this suggestion, made by our medical consultant, could not be confirmed or disproved. While the weakness and easy fatigability persist to this time, the blood pressure has remained normal for seven years and she can do her own housework. The diagnosis of posteclamptic hypertension is still the most likely. She was readmitted to St. Luke's Hospital five and one-half years later for a check-up. The insulin tolerance showed an abnormal sensitivity to insulin, the blood sugar being 71, 58, and 28 in one-half hour, at which time she had to be given orange juice because of hypoglycemic symptoms. No other test (Kepler-Wilder test or the water tolerance) showed any abnormality. The diagnosis of post-toxemic vascular damage with mild adrenal-cortical insufficiency was maintained.

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REVASCULARIZATION OF THE HEART

CLAUDE S. BECK, M.D., CLEVELAND, OHIO

(From the Department of Surgery, Western Reserve University and the University Hospitals)

THIS paper contains discussion of two points that were not in our recent publication.[1] One of these was omitted; the other is new information on the subject. In this paper I shall try to apply comparative values to various aspects of our work on revascularization.

Trigger Mechanism in the Heart.—The concept of "trigger" was a helpful guide in the experimental work. We found that local anoxia in the myocardium destroyed the coordinated contraction of muscle fibers and ventricular fibrillation appeared. Local anoxia was produced by ligation of arteries to an area of myocardium. As these small coronary arteries were ligated one after another, usually four or five of them, the area of myocardium supplied by these vessels became cyanotic and then a sudden fibrillation appeared. There seemed to be an analogy between this mechanism in the heart and a similar mechanism in the brain. Focal anoxia in the brain produces a convulsion of skeletal muscle; focal anoxia in the heart produces a convulsion of heart muscles. The one does not produce death; the other produces death.

We formed an opinion that generalized anoxia of the heart muscle was better tolerated than localized anoxia of myocardium. For purpose of illustration let us assume that it is possible to reduce arterial circulation by 25 c.c. of blood per minute. It appeared to us that this reduction in blood supply would be tolerated better by the heart if the reduction were made at the level of the common left coronary artery than if it were applied to either branch of this artery, and that either of the two major branches, that is, the descending or the circumflex arteries, would tolerate a reduction of 25 c.c. per minute better than if this reduction in flow occurred in the peripheral bed of myocardium. We do not have flow studies to support this belief but such studies, in my opinion, are not necessary. This idea conforms to laws of the circulation in general. Along this same line of thought is the idea of a marginal blood supply to a potential trigger. This term was used to designate that quantity of blood that held the trigger in abeyance, without which ventricular fibrillation occurred. To continue with this line of thought there were then two aspects to the coronary problem. One concerned total flow, the other concerned marginal flow. The one concerned continuous function of the heart and when reduced brought about heart failure with the usual signs of dyspnea and edema. The other, if I might be permitted to make this remark, could interrupt continuous function like turning off an ignition switch in a motor. It was a sudden disruption of function in a heart that was able to function under slightly improved conditions.

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In our experimental work we attempted to increase total blood supply (1) by grafting vascularized tissues to the surface of the heart with expectation of blood vessels growing across from the graft to the heart and (2) by converting the coronary sinus into an artery. To equalize distribution of blood so that it could do the heart the most good we attempted (3) to bring about the development of intercoronary channels. These intercoronary channels made it more difficult for "trigger zones" to develop. Communications between coronary arteries were produced by development of inflammation on the surface of the heart. Several thousand dogs were used in the development of this work, which was begun in 1932, which was interrupted for three years by the war, and which was begun again in 1945 and is in progress at the present time.

Measurements of Benefit.—To determine value or effectiveness of any experimental procedure in this work we ligated the descending ramus of the left coronary artery at its origin in one step and then determined results. Mortality rate and, in dogs that survived the ligation, the amount of destruction in heart muscle were determined. The results in fifty normal dogs were reported by Stanton, Schildt, and Beck.[2] Mortality was 70 per cent. In each dog that survived ligation a definite infarct was found. The destruction of heart muscle was always definite and extensive. Never was it possible to ligate this artery in a normal dog without definite destruction of heart muscle. A statement can be made concerning the value or effectiveness of these three methods. In order of importance, I would arrange these methods as 2, 3, and 1, with arterialization of the sinus as most effective and extracoronary communications as least effective. In the ten-year period before the war, Methods 1 and 3 were developed; Method 2 has been developed since the war.

Intercoronary and extracoronary communications together reduced mortality by one-half and also reduced the size of the infarct. We had a few specimens in which no infarct was present. Thirty-seven patients with severe coronary artery disease were operated upon using these methods. The clinical results were beneficial. Some of the patients were completely relieved of pain and were able to return to work. The clinical results confirmed the experimental studies.

Arterialization of the Sinus, Method 2 (Fig. 1).—The historical background of this work has been published and need not be repeated here. We developed an operation whereby arterial blood was delivered to the coronary sinus. This was accomplished in two ways: (1) by anastomosis between common carotid artery and coronary sinus, (2) by a free graft of vein between aorta and coronary sinus. After the technique of the operation was developed so that it could be done successfully the next step was to apply tests or measurements of benefit. We did sixty-seven experimental operations before we were able to make the first successful anastomosis. The development using carotid artery preceded the development of the free graft off the aorta.

Measurements of benefit applied immediately after anastomosis between carotid artery and coronary sinus: In these experiments the left common carotid artery was dissected free in the neck. It was transected and turned down into

the chest. Anastomosis between artery and coronary sinus was made. Immediately after the anastomosis was completed, the descending ramus of the left coronary artery was isolated and completely ligated at its origin. Our statistical records in these experiments were not entirely complete because our operative notes of the work two years ago when the experiments were done were largely a record of repeated failures. The approximate number of these experiments was six. There were five deaths and these occurred before closure of the chest was completed. There was one recovery. The heart in this dog showed a large infarct. Conclusion was made that under these experimental conditions, arterialization of the sinus was not beneficial. The measurements of results were the same as those obtained in normal control experiments. In 1938 Gregg and Dewald[3] reported results of their studies on the effect of arterial blood delivered to the coronary sinus. In these experiments arterial blood was delivered under pressure into the coronary sinus. These were acute physiologic experiments and, in so far as I know, were the first studies on this subject. The conclusion by Gregg and Dewald was that arterial blood delivered to the sinus did not have great value to the heart. The status of our work, then, at the end of six months of effort, was that there was no evidence of benefit by the anastomosis between coronary artery and coronary sinus. We then decided to place an interval of time between anastomosis and test of benefit.

Measurements of benefit applied two weeks after anastomosis between carotid artery and coronary sinus: Ten dogs with patent anastomosis were taken in this series. Two weeks after anastomosis was done the descending ramus of the left coronary artery was completely ligated at its origin in this series. Each dog made an immediate recovery. One died at the end of eight days, one died at the end of thirteen days, and eight dogs recovered. In a control group of ten dogs in which the anastomosis was blocked off by thrombus so that no blood passed through the anastomosis, death occurred almost immediately in seven and recovery occurred in three after this artery was ligated. The specimens in both series were examined for destruction of myocardium, ten specimens in the group with patent anastomosis and three specimens in the group with thrombosis. In the series with patent anastomosis there was no infarct in four specimens and in the remaining six the infarct was small. In no specimen was the infarct large and extensive. The three specimens of the control group each showed a large infarct. The infarcts in the two groups are shown in Figs. 2 and 3. These tests of benefit then indicate that arterialization of the sinus has great benefit to the heart after an interval of time. These results are definitely better than any results obtained in our previous work. It would appear that certain adjustments in the circulation take place after anastomosis and that time is necessary for beneficial effects to manifest themselves. We found that if heparinized blood is injected into the sinus in a retrograde direction, 9 c.c. per minute were recovered from the coronary artery in the normal dead heart. Two weeks after ligation of the sinus that figure was increased to 22 c.c. per minute. It would appear that the vascular bed in the heart opens up more freely after ligation of sinus and that adjustments take place after arterial anastomosis to the sinus has been made. These adjustments in the circulation invite further study.

Fig. 1.

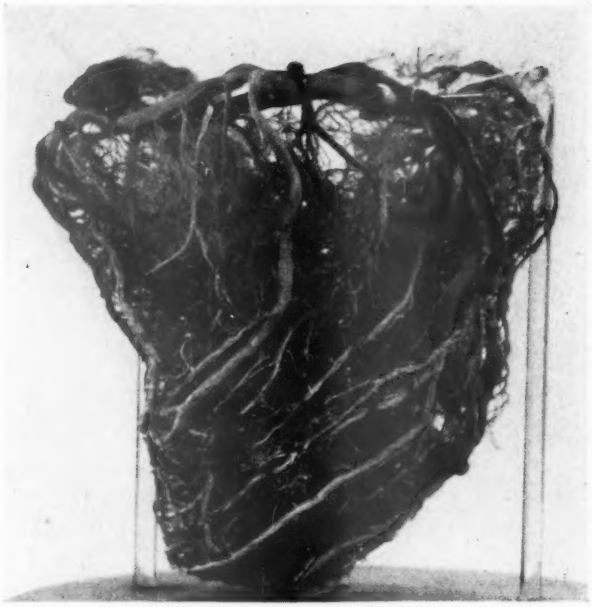

Fig. 4.

Fig. 1.—Beef heart. Arteries in red, veins in blue. Note rich vascularization. Communications exist between venous and arterial beds. These communications can open up so that arterial blood introduced into the venous system enters the arterial system where oxygen exchange is possible.

Fig. 4.—Dog heart. White vessel at base of heart is carotid artery grafted to coronary sinus. Specimen 4 months after anastomosis. Arteries in red, veins in white. Note communications between coronary sinus system and veins over right ventricle. These veins enter the right auricle. They may drain blood from coronary sinus system into auricle without going through capillary bed of left ventricle. These veins can be ligated.

Optimum Amount of Blood to the Sinus.—After measurements of benefit were obtained our thoughts turned to application to patients. We had been using the carotid artery in the dog. We decided that the carotid artery probably would not be satisfactory in man. It is larger than the coronary arteries and it is an important artery that cannot always be sacrificed without cerebral complications. There was no other available artery. The subclavian artery presented difficulties in the dissection and to get a sufficiently long segment to reach to the coronary sinus would involve ligation of collateral vessels for the arm. Decision was then made to use a free graft off the aorta. A free graft of artery or vein was used. More recently a graft of jugular vein was used in dogs. The technique of anastomosis was developed. Dogs died one after another after the graft was opened. Death occurred in the first twenty-four hours after anastomosis was completed. Frequently it occurred as the operation was

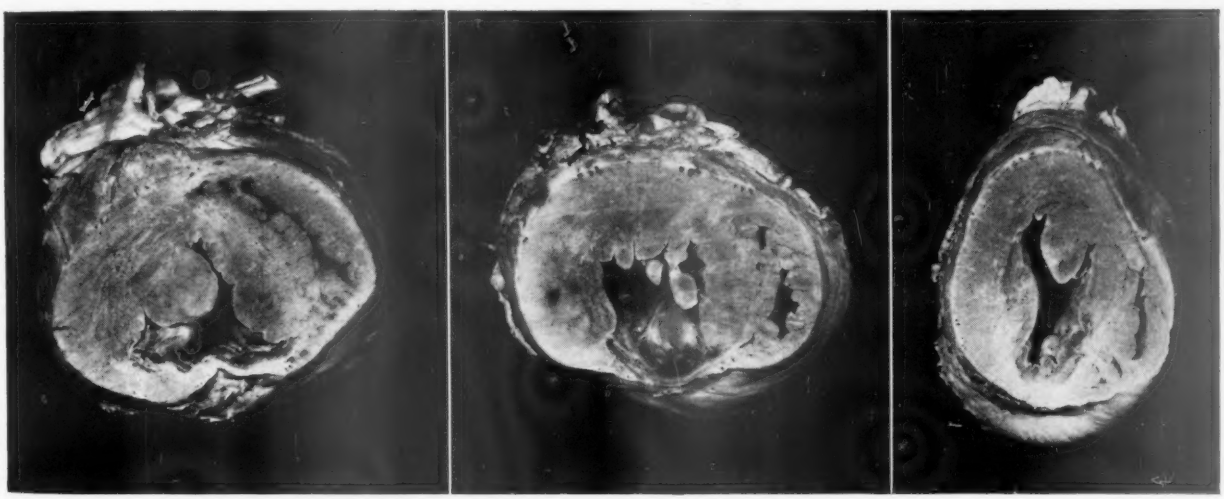

Fig. 2.—Control group of ten dogs. Ligation of descending ramus of left coronary artery at its origin. The mortality was 7, almost immediate in each. Recovery occurred in 3. The destruction of myocardium is shown.

being completed. The dogs that lived until the following day showed signs of heart failure. It was difficult for us to understand why these dogs died. They could tolerate the graft if carotid artery was used. They could not tolerate the graft if a free graft of jugular vein was used. The answer to this problem is simple now but it required several months of work before we proved that the jugular vein delivered too much blood to the heart. We constricted the jugular vein so that its lumen was about 3.5 mm. in diameter and the heart tolerated the graft of vein after it was constricted.

It would appear, then, that it is possible to deliver too much blood to the heart. This idea is, indeed, radical departure from established medical thought in reference to coronary artery disease. Always in the past appeared the idea of too little blood to the heart. Never, I dare say, was it even thought to be possible to deliver too much blood to the heart.

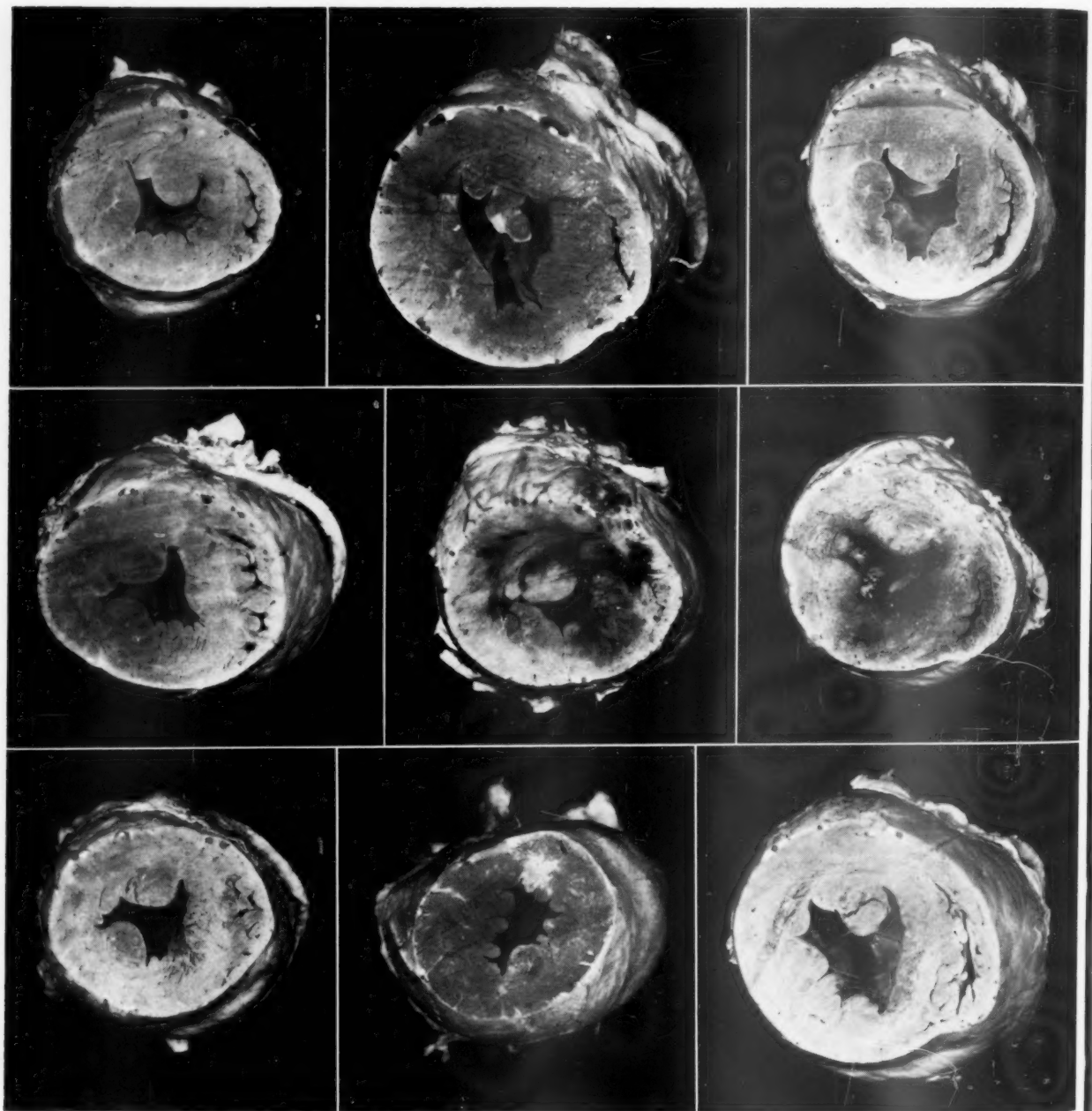

Fig. 3.—Anastomosis between carotid artery and coronary sinus. Two weeks later ligation of descending ramus of left coronary artery at its origin was done in a group of ten dogs. There was no immediate mortality. One died 8 days later, one died 13 days later and eight recovered. Nine of the ten specimens are shown. There is no destruction of myocardium in one-half the specimens. In no specimen is the destruction extensive as in the control group.

DISCUSSION

In retrospect there were several conditions that could have prevented the development of this work. One was the size of the graft and the amount of blood delivered to the sinus. It was fortunate that we used carotid artery in the early experiments because the amount of blood delivered by the carotid artery was tolerated by the heart. Had we used a graft of jugular vein the heart would not have tolerated the flow. It would have been necessary to constrict the vein in order to get recovery. I do not know whether we would have constricted the vein if we had not known that the carotid artery was tolerated. Another condition that had to be dealt with correctly in order to develop this work concerned the interval of time between anastomosis and ligation of coronary artery for test of benefit. As stated elsewhere, there was no immediate benefit after the anastomosis was opened and an interval of time was necessary in order to obtain beneficial measurements for the operation. This step was essential for the development of the work. A third condition that determined progress was the condition of the virginal sinus. The normal sinus is so delicate that it cannot be sutured in most experiments. After it had been ligated for seven to ten days it became thicker and could be handled more safely at operation. Preliminary ligation of sinus became almost a requirement for success.

Comparative Values Applied to Various Aspects of Arterialization of Sinus.—Consideration of *primary* importance. This is the value of arterial blood in the sinus. No other aspect of this subject has equal importance.

Considerations of *secondary* importance:

1. Method by which arterial blood is directed into sinus. We used two methods. Other methods may be developed.

2. Thrombosis. We can usually predict at the time when anastomosis is made whether it will remain patent. We are familiar with the factors that determine thrombosis. We have made approximately fifty patent anastomoses to date.

3. Amount of blood to the sinus. We know that an excessive amount of blood can be delivered to the sinus and no doubt there is an optimum amount. In patients with coronary artery disease one would expect that the amount entering the coronary arteries might be a factor in the optimum flow for the heart through the graft. For the dog with the coronary arteries not occluded we found that the amount delivered by the common carotid artery could be tolerated; we found that the jugular vein off the aorta was not tolerated. We found that if the jugular vein was constricted to about the size of the carotid artery that the heart did tolerate this flow. For the patient with coronary artery disease it would appear to me that the graft should be constricted to about 4 mm. in diameter.

4. Arteriovenous fistula. The coronary sinus system of veins has a variable number of communications that flow independently into the right auricle (Fig. 4). Will these veins drain off blood so that blood will escape the capillary bed of the left ventricle thus establishing fistulous communications? This possibility exists. We believe that there is an optimum flow to the sinus and that there is a

ceiling for inflow which should not be exceeded. The inflow will be fixed by constricting ligatures on the graft so that inflow cannot become progressive with time as happens in patients with congenital arteriovenous fistulas. Therefore, I assume that this development of drainage channels will reach a maximum and then the development will stop. Perhaps these veins may be beneficial in draining excessive amounts of blood from the venous system. It may be possible to occlude these veins by ligation if they reduce the effectiveness of the new circulation. To my mind the problem of fistulas is of secondary importance. I believe these venous communications can be modified or controlled if necessary.

5. Disease in the aorta. It is possible for disease of the aorta to preclude making anastomosis between aorta and graft. Such cases would be exceptional.

6. Can patients with severe coronary artery disease tolerate the operation? We know that this type of patient is not a good risk for any operation. A number of patients who offered themselves for this operation have died without any operation having been done. As Dr. Gallie recently stated in his presidential address to the American Surgical Association: "Surgeons are engaged in trying to do a large amount of good and a small amount of harm." In reference to patients with coronary artery disease these two factors will have to be balanced one against the other.

Additional considerations might be mentioned and, no doubt, additional problems will appear in the future. Further experimental studies and, at the proper time, application to patients, no doubt, will bring to light additional problems that will need solution. For the present I think we can accept the measurements of arterial blood in the coronary sinus as indicating substantial benefit and with this as a background I feel we should go ahead and try to solve the secondary problems leading to application to patients with coronary artery disease. Up to the present time we have operated upon one patient and we are almost ready to go ahead with application to additional patients.

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HYPERHIDROSIS

Observations on the Study of Sixty-one Cases

J. Ross Veal, M.D., and John N. Shadid, M.D., Washington, D.C.

(From the Department of Surgery of the Georgetown University School of Medicine)

HYPERHIDROSIS, or pathologic excessive sweating, is part of a symptom complex caused by abnormal stimulation of the sympathetic nervous system. It is usually accompanied by vasoconstriction, and persistence of the condition may lead to certain vascular complications. It is relieved by interruption of the sympathetic pathways. A study of sixty-one cases forms the basis of this report.

The sympathetic nervous system exerts a profound influence, directly or indirectly, on all physiologic functions, and among these is the control of the peripheral blood vessels and sweat glands. With centers located in the hypothalamus, and possible connections higher up in the brain, sympathetic pathways extend down through the intermediolateral cell column of the spinal cord. From there, branches pass out in a segmental manner to the ganglionated chain as white rami and from the ganglia as gray rami to the peripheral nerves. From these, nerve fibers are distributed to the blood vessels and sweat glands. They supply both vasodilator and vasoconstrictor fibers to the vessels, and the volume blood flow is controlled by stimulating or depressing the impulses. Stimulation of the sympathetics increases sweat secretion, while blocking them checks sweating. These responses are so balanced normally that there can be excessive sweating without vasoconstriction, and vasoconstriction may occur without sweating, depending on the immediate needs of blood flow and perspiration.

The main functions of sweating is to keep the skin moist and pliable and to aid in the regulation of body temperature, the latter function being controlled by the heat-regulation center. Thus a thermal stimulus of increased internal or external temperature brings into action the mechanism for cooling the body and results in generalized cutaneous vasodilatation and increased sweating. A different type of stimulus is that of mental stress brought about by concentration, fear, anxiety, anger, and pain which alerts the emergency mechanisms of the body through generalized sympathetic stimulation. The normal response to this stimulus is increased sweating, particularly of the palms and soles, vasoconstriction, tachycardia, rise in blood pressure, increased respirations, and pilomotor activity. In certain types of abnormal stimulation or from increased sensitivity of the sympathetics, some of these normal reactions are so exaggerated that a distinct pathologic entity is produced. The observations recorded in the study of sixty-one such cases will be described.

In this group of cases excessive sweating with beads of sweat collecting and dripping off the skin was a constant feature. Vasoconstriction was almost constantly present. Other manifestations such as tachycardia, vasomotor insta-

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bility, emotional imbalance, and an inner tenseness were often observed, depending on whether or not the sympathetic stimulus was central or peripheral in origin. Adson, Craig, and Brown[1] noted such manifestations in their case reports of hyperhidrosis in 1935. It seems that the term hyperhidrosis, which is only a symptom, is incorrect in classifying this disease. We propose to use the more descriptive term hypersympathotonia for this symptom complex. This implies that through abnormal stimulation normal sympathetic responses are exaggerated to the point of being pathologic in character.

ETIOLOGY

Hypersympathotonia, or excessive stimulation of the sympathetic nervous system, may occur under a variety of conditions. It may involve the entire sympathetic system or only a portion of it, depending on the origin of the stimulus. When the stimulus originates in the brain centers, the hypothalamus having been shown to be the most important, it will affect the entire sympathetic system. It is usually a functional disorder. Rarely does an organic lesion of the brain such as tumor, trauma, or inflammatory disease cause hypersympathotonia.

When the exciting stimulus arises from levels below the brain, the cause is usually organic in character. Trauma or inflammatory lesions involving the cord, peripheral nerves, or blood vessels may provide the stimulus. Hypersympathotonia has resulted from poliomyelitis, peripheral neuritis,[2] direct trauma to the cord or peripheral nerves, neuroma,[3] inflammatory diseases of the peripheral vessels, and frostbite of the extremities. An interesting localized type is that which accompanies local inflammatory lesions about the extremities.

CLASSIFICATION

Since the etiology of hypersympathotonia is not clear in the majority of cases, it is not possible to give an accurate classification. From the analysis of sixty-one of our cases the classification is given in Table I.

The cases may be divided into two large groups: primary and secondary hypersympathotonia.

In the primary form there is no known organic lesion causing the symptom complex, and the entire sympathetic system is affected. It usually manifests itself early in life and may be congenital or acquired. Our youngest patient was 8 months old; the oldest was 70 years of age. It is often familial in character. In our series there have been as many as five members of one family affected, three in another, and two in several families. Female subjects are affected more often than male.

The group classified as secondary hypersympathotonia includes those patients in whom the disease followed some known exciting cause. Usually only part of the sympathetic system is involved. The exciting cause has been either an injury or an inflammatory process involving some part of the peripheral nervous or vascular systems. The traumatic nerve injuries are usually not severe enough to cause paralysis. In one of our patients a fracture of the cervical

TABLE I. CLASSIFICATION OF HYPERSYMPATHOTONIA (PATHOLOGIC HYPERHIDROSIS) ANALYSIS OF SIXTY-ONE CASES

Primary		
Total cases		41
Female	28	
Male	13	
(General involvement in all cases)		
Secondary		
A. Associated with vascular disease		10
1. Post frost-bite	6	
(Bilateral lower extremities, 6)		
Female 2		
Male 4		
2. Post-thrombophlebitis	4	
(Single lower extremity, 4)		
B. Traumatic		4
Bilateral upper extremity	1	
Unilateral upper extremity	2	
Bilateral lower extremity	1	
Female 1		
Male 3		
C. Associated with scleroderma		1
Female		
D. Postsurgical menopause		1
Female		

vertebrae did cause compression of the cord and resulted in permanent paralysis of the lower part of the body. The symptoms of excessive sympathetic stimulation involved only the upper quadrant of the body and probably was a compensatory reaction. This patient developed marked hyperhidrosis of the face, neck, and upper extremities. Peculiarly, each day at about the same hour either one or the other side would break out in great beads of sweat. This would last several hours and then dry up and the opposite side would begin to sweat. The other traumatic cases have resulted from milder injuries of the peripheral nerves. In none of these patients were there any signs of disturbed sensory or motor function of the involved nerves, yet they presented marked sympathetic stimulation distal to the sites of injury. The patients with associated vascular diseases (secondary group) have all shown varying degrees of inflammation of the vessels in the involved parts. Notably among these have been thrombophlebitis and frostbite. All of these patients have exhibited a strong reaction to vasoconstrictor influences in other parts of the body.

Four of our patients presented localized sweating of a small area of the legs over a chronically inflammed region. Biopsy from one of these showed a diffuse subacute inflammation of the skin and fat pad and a perivascular infiltration of the small vessels. The final two secondary cases were general in character, one scleroderma and the other following surgical menopause.

SYMPTOMS

Regardless of the etiology or parts involved, hypersympathotonia has certain characteristics. The essential differences between the symptoms of the primary and secondary types are mainly in the extent of involvement. In neither group have the sympathetic ganglia been found organically diseased.

In the primary form the condition may be so mild that for years little attention is paid to it. Then under some new stress and strain it becomes mark-

edly disturbing. Several of our patients presented a history of mild hypersympathotonia from childhood, and on being placed in the military service their symptoms became so aggravated that they received medical discharges. In others the symptoms were of little consequence until the patient reached adolescence. In some the stress of earning a living in a competitive business world caused such marked increase in severity of symptoms that they had to give up their work.

The main signs are excessive sweating and vasospasm. These signs are intermittent and remittent. All sympathetic irritants cause aggravation of the symptoms. Chief among these are fatigue, mental anguish, smoking, anxiety, and pain. It has been noted that these patients can be induced to sweat with tests that do not ordinarily affect normal individuals. We have found that scratching the skin with a sharp needle or performing a venipuncture may induce profuse sweating and marked vasospasm in these patients. Intradermal injections of a weak solution of pilocarpine will cause widespread sweating in the immediate area of the injection (Fig. 1). A weak nicotine solution will also produce such a reaction. The medial aspect of the foot is a good region to apply these tests (Fig. 2). In order to picture the intensity of sweating, the Minor[4, 5] test* is quite useful (Figs. 2 and 3).

It is the excessive sweating that has been most distressing to the majority of these patients. The sweating is usually intermittent. During certain periods of the day the sweating may subside and all seems well. Then suddenly beads of sweat begin to form, coalesce, and drip from the skin. Although sweat glands are distributed over practically the entire surface of the body, the hands, feet, and forehead have the greatest number per square inch.[8] Under normal conditions these areas most abundantly provided with sweat glands do not sweat most profusely,[8, 9] but in the primary form of hypersympathotonia these areas show the most activity. In the secondary form the excessive sweating is limited to the area stimulated.

The usual stimuli which produce normal excessive sweating also cause excessive sweating in the hypersympathotonic subject. In fact, these subjects respond more profusely and more readily to high temperatures and muscular exercise. A striking difference between the normal subject and the person with hypersympathotonia is the reaction to a cold environment. Normally, when the temperature of the environment falls to 70° F., sweating is at a minimum, and on lowering the temperature further, sweating ceases. The person with hypersympathotonia, on the other hand, may sweat profusely at a temperature of 70° F. and may continue to sweat at even lower temperatures.

The majority of our patients showed signs of vasospasm. Vasoconstriction is more evident in a cool environment. When examined at a room temperature of 68° F., these patients have exhibited varying degrees of cyanosis of the nail beds of the fingers and toes. This sign was usually more marked in the lower

*Minor test: Solution is made up of the following constituents: Iodine 1.5—2 Gm., castor oil 10 c.c., absolute alcohol to 100 c.c. This solution is applied to skin that is clean and dry and the area is dusted with fine starch powder. In the presence of sweat the starch-iodine reaction will result, giving a blue-black to violet-black color.

extremities. Often, blotchy cyanosis extended up to the trunk. In none of these patients has there been blanching of the digits as seen in Raynaud's disease. Arterial pulsations of the pedal vessels were often diminished and not demonstrable in some. In several the disability from impaired circulation led

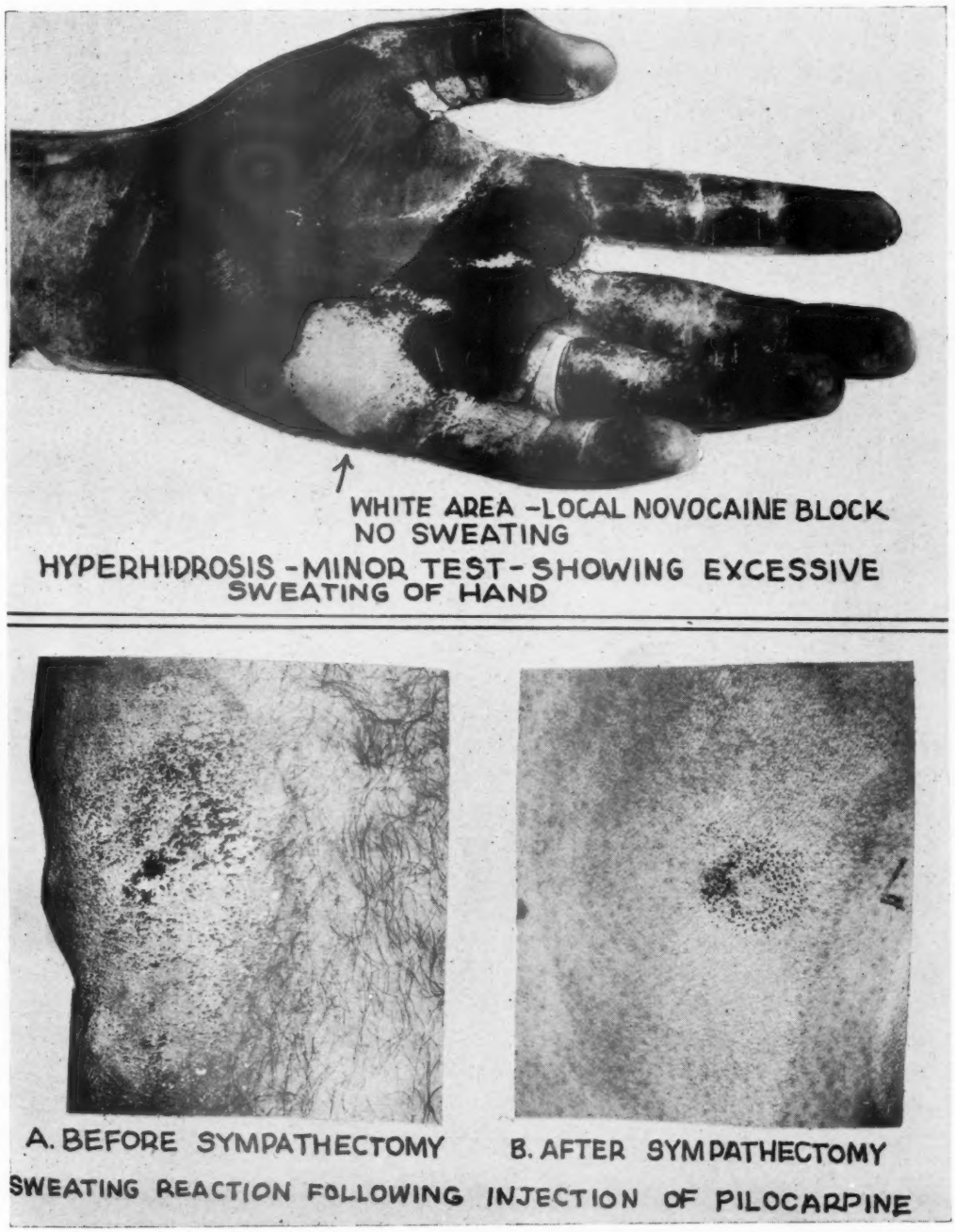
WHITE AREA -LOCAL NOVOCAINE BLOCK
NO SWEATING
HYPERHIDROSIS - MINOR TEST - SHOWING EXCESSIVE SWEATING OF HAND
A. BEFORE SYMPATHECTOMY
B. AFTER SYMPATHECTOMY
SWEATING REACTION FOLLOWING INJECTION OF PILOCARPINE

Fig. 1.—Excessive sweating of hand demonstrated by Minor test. Note small nonsweating area. Sweating was abolished temporarily by local Novocain infiltration. In lower frame, *A* shows sweating reaction to pilocarpine when injected intradermally before sympathectomy. *B*, same test after sympathectomy.

them to seek medical advice. In those patients with severe spasm, impaired circulatory manifestations were noted. These included easy fatigue, night cramps in the legs, intermittent claudication and occasionally venous thrombosis. In several of the patients a diagnosis of thromboangiitis obliterans had been made. Biopsies of the vessels and response to treatment proved such a diagnosis incorrect. Local skin infections were common and several patients

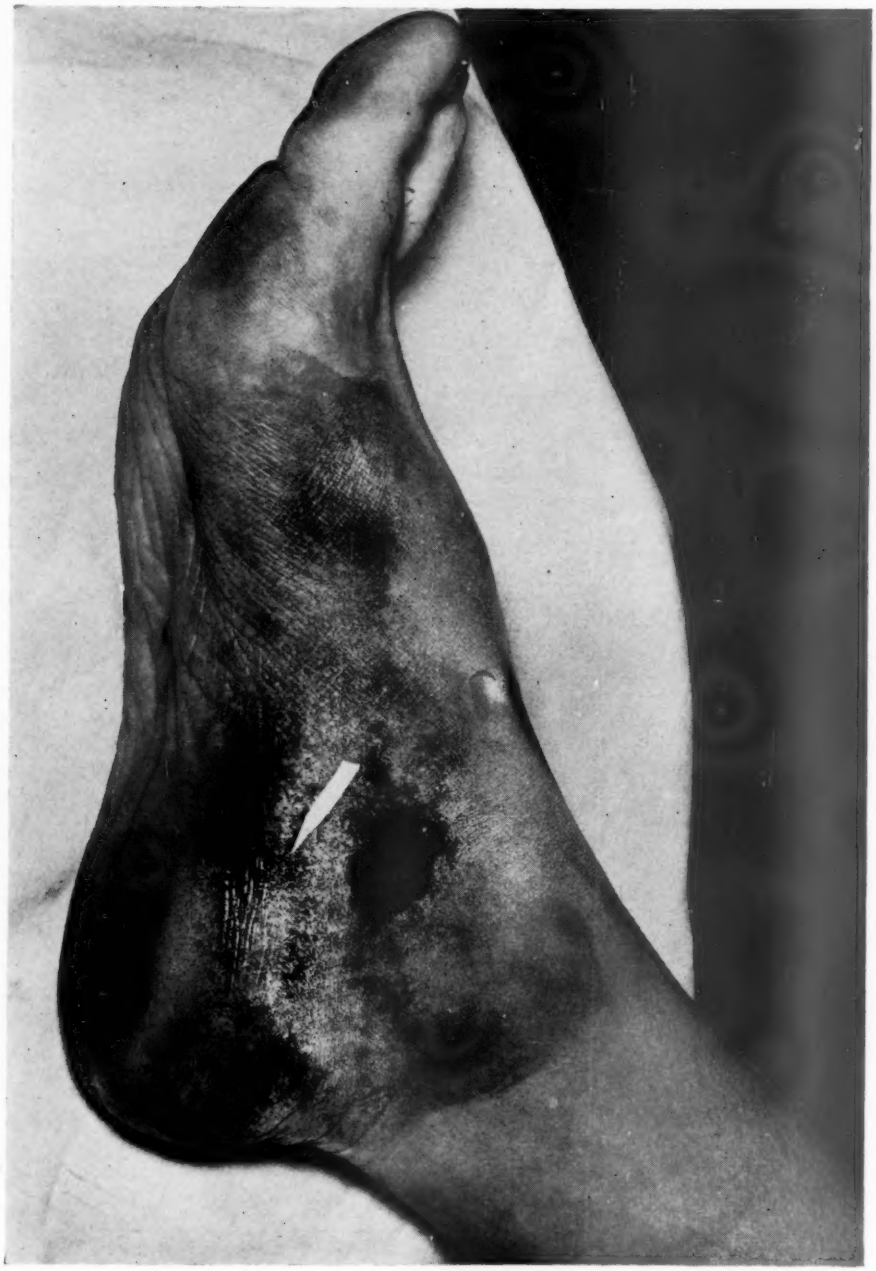

Fig. 2.—Local sweating reaction to pilocarpine intradermally. Arrow point shows sight of injection. Minor starch test shows widespread sweating.

had developed chronic lymphangitic edema. Local infections and injuries invariably were slow to heal and often caused exacerbation of sweating and vasoconstriction.

INDICATIONS FOR SURGERY

Sympathetic interruption causes local vasodilatation and checks normal as well as excessive sweating. According to White,[10] the first attempt at neuro-

HYPERHIDROSIS IN THROMBOPHLEBITIS MINOR TEST SHOWING SHARP LIMITATION OF SWEATING AREA (ARROW ABOVE)
SAME CASE SHOWING BEADS OF SWEAT COLLECTING ON SKIN

Fig. 3.—Excessive sweating in superficial thrombophlebitis. Note that sweating is limited to the inflammatory zone of thrombophlebitis. In upper right portion a section from photograph of leg shows great beads of sweat.

surgical treatment for hyperhidrosis was performed by Kotzareff in 1919. The operation was partial resection of the cervical ganglia for unilateral hyperhidrosis of the face. In 1935 Adson, Craig, and Brown[1] reported the success of sympathectomy in the treatment of hyperhidrosis. List and Peet[5, 6, 7] have added to our knowledge of the regional sympathetic nerve distribution to the sweat glands. There are many reports demonstrating the success of sympathectomy in the treatment of this condition. However, many patients suffering from this disease are denied the benefit of sympathectomy. This may be because the physician has not been informed of its success or may feel that sympathectomy is yet a too radical procedure.

There are many mild cases of hypersympathotonia that do not require any form of treatment. Some of these persons may have bouts of exacerbations during periods of intense stress and strain which usually subside when equanimity is restored. Certain persons, however, have such marked symptoms which are so persistent that they become a real handicap. Excessive sweating of the hands may become a social and occupational handicap. Several of our female patients found that they were so embarrassed by their cold, sweating hands that they refused all forms of social activities. One young lady carried six pairs of white cotton gloves to her dances and changed them frequently as they became damp. A young artist failed in his first professional job because he spoiled all of his drawings by dripping sweat. Some were unable to wear hose because their legs and feet were always wet. One young lady ruined twenty-three pairs of shoes in one year through excessive sweating of the legs and feet. In some of our cases vasospasm had reached such a degree that symptoms of impaired circulation were quite disturbing. Fatigue of the lower extremities was a common finding. In several there was actual intermittent claudication. There were also several instances of venous thrombosis resulting from persistent vasospasm. These severer forms of hypersympathotonia, we believe, should have the benefit of sympathectomy.

RESULTS OF SYMPATHECTOMY

In this series of sixty-one patients there were only twenty-three subjected to surgery for a total of seventy-two operations (Table II).

TABLE II

	CASES	OPERATIONS
Combined bilateral cervicodorsal and lumbar sympathectomy	14	56
Lumbar sympathectomy (Bilateral, 6; one extremity, 1)	7	13
Cervicodorsal (Bilateral, 1; one extremity, 1)	2	3
Total	23	72

We have used the preganglionic cervicodorsal sympathectomy[11] for the upper extremities, and for the lower extremities the second, third, and fourth lumbar ganglia have been resected. The end results have been uniformly good and the symptoms have been relieved. There has been no recurrence of sweating. The sweat glands, however, still retain their ability to function. In extreme high

environmental temperatures mild sweating can be demonstrated in the sympathectomized areas. Pilocarpine will also produce sweating but to a very mild degree (Fig. 1). Nicotine fails to excite sweat gland activity. However, smoking may cause vasoconstriction. In three patients in whom a bilateral cervicodorsal sympathectomy was performed there has been a recurrence of mild vasospasm in one of the upper extremities. This has been added proof of the presence of vasoconstriction in hypersympathotonia and probably resulted from an incomplete sympathectomy. In all of the remaining patients the vasospastic symptoms have been alleviated. The fatigue, night cramps, and intermittent claudication have been relieved.

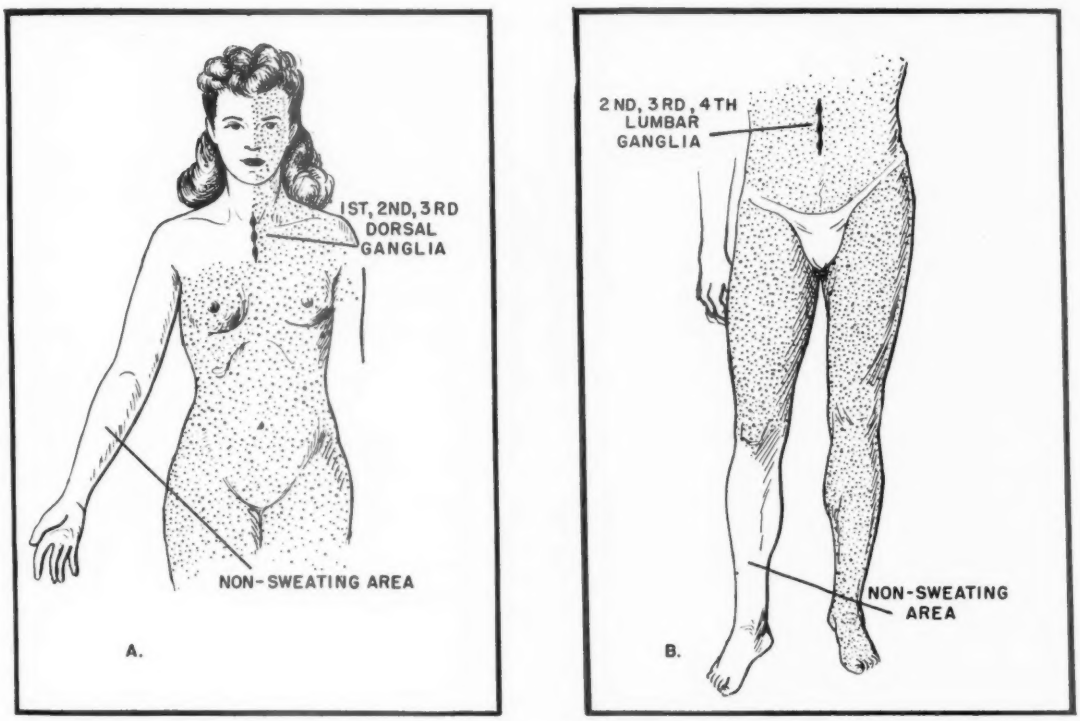

Fig. 4.—Showing "dry areas" following cervicodorsal and lumbar sympathectomy. The sweating area is diminished and may function excessively under proper stimulation. *A*, Area controlled by first, second, and third dorsal ganglia; *B*, area controlled by second, third, and fourth lumbar ganglia.

Special comment should be made about those patients in whom a quadrilateral sympathectomy was done. These operations, of course, deprive the patient of a large number of actively functioning sweat glands. The operations checked sweating of the arms, upper chest, neck, and head. If we add to these areas those eliminated by bilateral lumbar sympathectomy, the feet and legs, the "dry portion" of the body surface is quite extensive (Fig. 4). That portion of the body in which the nerve supply to the sweat glands remains intact responds to certain forms of sympathetic stimulation by sweating excessively. This has been quite a problem for a few of our patients in the hot and humid summers of Washington. Those employed in occupations that require consider-

able muscular activity have also witnessed some discomfort from excessive sweating of the trunk. Usually after a year or two sweating becomes more normal.

SUMMARY

A study of sixty-one cases of hyperhidrosis has been presented. The essential abnormality is excessive stimulation of the sympathetic nervous system or an increased sensitivity of this system. Excessive sweating has been the predominant symptom, but other signs of sympathetic irritation have usually been present. For this reason we have suggested the term hypersympathotonia to describe this pathologic entity. The etiologic factors have been discussed and a simple classification has been offered. The reasons for selection of certain cases for sympathetic surgery have been submitted. Finally, the results of sympathectomy have been presented.

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PORTACAVAL ANASTOMOSIS FOR PORTAL HYPERTENSION

ARTHUR H. BLAKEMORE, M.D., NEW YORK, N. Y.

(From the Department of Surgery, the Presbyterian Hospital)

THE control of gastrointestinal hemorrhage and ascites secondary to portal hypertension has long constituted a problem.

Encouraged by early successes in the establishment of portacaval shunts, this series has gradually been expanded to embrace sixty cases.

In the early cases, the nonsuture Vitallium tube method was employed. Noting the tendency of some of the earlier anastomoses to undergo gradual fibrotic occlusion, a shift was made to the suture method. The latter method has long since been employed exclusively. It has the added advantage of conserving the kidney in the splenorenal type of portacaval shunt.

In sixteen of the sixty cases in which portacaval shunts were established (approximately 25 per cent), the functional and pathologic status of the liver was essentially normal. In this group portal hypertension was secondary to a block in the portal bed outside of the liver.

The portal vein itself is so frequently the seat of the obstruction in this type of case as to make one rely primarily upon anastomosis of the splenic vein, end-to-side, with the left renal vein for the establishment of a portacaval shunt. This fact alone makes splenectomy contraindicated in such cases, unless the surgeon is prepared at the time to proceed with a splenorenal shunt following removal of the spleen. Approximately one-half of the shunt failures (twelve in all for the series) are attributable to attempts to save post-splenectomy bleeders. Though to include this group gives a less favorable impression to the over-all results, it is believed that exploration should be carried out in the patient who is a post-splenectomy bleeder with the possibility of establishing some type of portacaval shunt. The likelihood of success is in the neighborhood of 50 per cent.

Upon exploration of the post-splenectomy bleeder one will not infrequently find that there is a portion of the stump of the splenic vein remaining unclotted, sufficiently long to effect an end-to-side anastomosis with the vena cava. The inferior mesenteric vein is sometimes sufficiently large to anastomose (proximal) end-to-side with the left renal vein. Or, more frequently, the superior mesenteric vein has been employed. The latter, though technically more difficult, should be employed preferably in side-to-side anastomosis with the vena cava.

Portal hypertension secondary to cirrhosis of the liver constitutes, in a number of cases, by far the greatest problem. Fortunately, in this great group, one has an extra choice in vessels, its being possible to employ the portal vein itself in effecting a portacaval shunt.

A decade of experience with the modern medicodietary regimen in the treatment of portal (Laennec's) cirrhosis of the liver has now fairly well

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established what can and cannot be accomplished. In respect to the incidence and severity of gastrointestinal hemorrhage, for example, I am informed by Dr. Arthur Patek, who has been a pioneer in this field, that once a patient with cirrhosis has a hemorrhage he has but a 50 per cent chance of being alive one year hence.

Perhaps the greatest achievement of the modern medical regimen in the treatment of Laennec's cirrhosis has been in the relief of ascites. But, here too, there are treatment failures, and in many of this group, the persistence of the ascites is due to the presence of portal hypertension.

There is a growing unanimity of opinion that the medical treatment of post-hepatitis cirrhosis is not so satisfactory as that of cirrhosis of the Laennec type. However this may be, we are seeing in ever-growing numbers cases of post-hepatitis cirrhosis in which portal hypertension plays the decisive role.

The portacaval shunt has proved to be a direct and efficient method of reducing portal hypertension in cases of cirrhosis of the liver. With reasonable care in the selection of cases, preoperative preparation, and postoperative handling, the procedure can be accomplished without unreasonable risks. As a matter of fact, in the ten cases in which the portal vein was anastomosed to the vena cava, there has been only one postoperative death.

From the standpoint of affording maximum reduction of portal blood pressure, the portal vein, because of its larger size, is preferable to the splenic vein in the establishment of portacaval shunts in cases of cirrhosis of the liver. The complete disappearance of esophageal varices has been noted as demonstrated by x-ray examination following the establishment of portal vein-to-vena cava anastomoses.

We are convinced that the portal vein-to-vena cava type of portacaval shunt has a much higher chance of sustained patency than the splenorenal type of portacaval shunt. There are several logical reasons for this, based upon accurate observations.

In the first place the portal vein has a far huskier wall than the splenic vein. It is not necessary to explain what this means to surgeons who have attempted to anastomose veins. This fact, plus the supported position of the portal vein within the hepatoduodenal ligament, enables it to withstand prolonged periods of portal hypertension without undergoing degenerative changes. In contrast, the thinner walled, relatively unsupported, splenic vein when subjected to a rise in portal pressure becomes dilated, elongated, and tortuous. Degenerative changes in the wall, consisting of areas of atrophy to tissue paper thinness, and the development of intimal sclerotic plaques appear relatively early.

In performing the splenorenal anastomosis there is more likelihood of twisting the splenic vein or the occurrence of angulation compression than obtains in performing the portal vein-to-vena cava type of portacaval shunt. In mobilizing the splenic vein, unlike the portal vein, it is necessary to ligate many branches which penetrate the pancreas. The latter is a vascular organ and hemorrhage must be controlled with suture ligatures. Aside from the

many ligated branches affording a nidus of thrombus within the splenic vein, the mass ligatures in the pancreas introduce another possible hazard. As has been frequently observed, the splenic vein lies, for a portion of its length, in a sulcus upon the pancreas. This places the thin-walled vessel in direct contact with areas of pancreatic tissue which have been strangulated by suture ligatures. Opportunities have presented to observe that there can be fibrous tissue residual in these areas, which raises the question of possible late compression of the splenic vein itself.

Though the comparative advantages of the portal vein-to-vena cava type of portacaval shunt were early appreciated, it was used with extreme caution. There are now four patients with portal vein-to-vena cava anastomoses, end-to-side, who have been followed in excess of two years. No essential differences have been noted in the behavior of the cirrhotic livers from comparative cases in which the splenorenal type of portacaval shunt has been employed. Thus being reasonably sure of the ground, the use of the portal vein in cases of cirrhosis of the liver has more recently been expanded.

In June, 1947, while watching Heeney and Humphreys do a complicated surgical procedure through a right thoracoabdominal approach, I was impressed by the good lateral exposure of the hepatoduodenal ligament and the ready access to the vena cava. The good exposure was largely accounted for by partial section of the diaphragm, permitting rotation upward of the dependent anterolateral margin of the liver. Needless to say, the thoracoabdominal approcah through the right diaphragm was promptly employed for the establishment of portal vein-to-vena caval shunts with satisfaction in proved cases of cirrhosis of the liver.

I have recently presented a technique for side-to-side anastomosis of the portal vein to the vena cava. The method has been employed in two cases with satisfaction. In one case an esophagram done before discharge of the patient from the hospital revealed complete disappearance of the esophageal varices. The second patient is doing well, but has not yet been discharged.

The side-to-side type of anastomosis would seem to offer two theoretical advantages over the end-to-side anastomosis of the portal vein to the vena cava, namely, (1) it permits portal blood flow through the liver, should ever the pressure relations become conducive to flow; (2) a lessened tendency to thrombosis of the portal vein toward and into the liver. The side-to-side variety of anastomosis would seem to eliminate any possible objection to the routine employment of the portal vein-to-vena cava type of portacaval shunt for the relief of portal hypertension in proved cases of cirrhosis of the liver.

A review of the entire series of sixty cases in which portacaval shunts have been established offers encouragement from the successes, which, fortunately, are decidedly in the majority. The real milestones of progress in the experience, however, mark those instances of failure presenting overt evidence of errors in judgment or technique.

The operations were performed by either Dr. Allen Whipple or myself in 50 of the 60 cases with a loss of 8 cases postoperatively. There were 3 post-

operative deaths in the 10 remaining cases of the series, bringing the total to 11 deaths for the entire series of 60 cases. Death in the 3 cases from mesenteric thrombosis would, on the basis of necropsy findings in 2, appear to be due to retrograde thrombosis from cavernomatous changes in the portal vein in one case, and an ascending thrombophlebitis starting in the hemorrhoidal veins in the other case.

In 8 postoperative deaths, the cause of death was as follows: cerebral damage, 2 cases, 1 of cerebral thrombosis, 1 of lenticular degeneration (Wilson's disease); cardiac failure, 1 case; shock from intraperitoneal hemorrhage, 1 case; gastrointestinal hemorrhage, 1 case; cholemia, 3 cases.

Considering that there were forty-three cases of cirrhosis of the liver in the group, the most impressive feature of the entire death analysis is the low incidence of death from liver failure.

In 1940, Dr. Robert S. Grinnell reviewed the cases of cirrhosis of the liver at the Presbyterian Hospital in which simple omentopexy operations had been performed. There were some forty odd cases in the series and the hospital mortality approached 50 per cent. This contrast attests to the very real progress that has been made in recent years both in preparing the cirrhotic liver for surgery and protecting it from damage during operation.

In viewing follow-up results following the portacaval shunt procedure in cases of cirrhosis of the liver, one must keep in mind exactly what can logically be expected of the operation. In the present state of knowledge, at least the procedure can be expected to alter the natural history of cirrhosis in so far as it modifies the course of intractable, wasting ascites, and recurring hemorrhage secondary to portal hypertension.

A TECHNIQUE FOR DIVISION AND SUTURE OF THE PATENT DUCTUS ARTERIOSUS IN THE OLDER AGE GROUP

NORMAN E. FREEMAN, M.D., FRANK H. LEEDS, M.D., AND
RICHARD E. GARDNER, M.D., SAN FRANCISCO, CALIF.

(From the Division of Surgery and Laboratory of Experimental Surgery, University of California Medical School)

GROSS[1] who performed the first successful ligation of a patent ductus arteriosus, again led the way by proving that dividing the ductus was a more effective procedure than ligation.[2, 3] Surgeons with experience in this field have confirmed his teachings.[4-7] Thus, patients with patent ductus arteriosus are offered an escape from the inevitable incapacitation and shortening of life which result from this malformation.[8-12]

These brilliant results have occasionally been complicated by serious hemorrhage at the time of operation.[2, 4, 6, 10, 13, 14] We felt that this danger could be decreased by handling a patent ductus arteriosus as we would any other arteriovenous fistula; that is, by control of the arterial and venous components before approaching the communication. This would entail, first, control of the circulation through the artery and the vein above and below the fistula; second, division of the connection between artery and vein; and third, separate repair of the defects in the artery and vein.

Johnson, Jeffers, and Margolies[15] first suggested that, in the management of a torn ductus arteriosus, the pericardial sac should be opened and a piece of hernia tape placed loosely around the pulmonary artery in the same manner as for a pulmonary embolectomy. If bleeding should be profuse at any time, it could be controlled momentarily by compressing the main pulmonary artery. Neuhof[16] pointed out that the source of hemorrhage was the posterior surface of the ductus and the cause, in addition to the possible or probable friability of the ductus when it was the seat of endarteritis, was the difficulty of dissection in this region. It was apparent that the exposure of the ductus would be facilitated by incising the pericardium and retracting the dilated pulmonary artery. He accomplished this technique successfully in three cases. Wangensteen[7] also employed this technique in difficult cases. While ligating a patent ductus arteriosus Crafoord[4, 14] had the experience of having the ligature cut through with bleeding from both the pulmonary artery and the aorta. To control the bleeding it was necessary to apply clamps across the aorta above and below the origin of the ductus and to apply a clamp to the side of the pulmonary artery. Since then he has successfully used this technique, originally forced on him, in thirty-five cases. He feels that it is possible thus to excise all the ductus tissue out of the aortic wall. Normal aortic wall edges can then be sutured. This technique is safer than leaving behind tissue which might later cause difficulty by forming an aneurysm.

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It has been found in two cases of surgery of the abdominal aorta, one for arteriovenous fistula[17] and one for aneurysm of the aorta,[18] that prolonged occlusion of the aorta above the renal arteries may lead to a temporary postoperative suppression of renal function associated with transient hypertension. Though Crafoord[4] reported no evidence of renal damage with his technique of clamping the aorta, he did report one case in which the aorta was clamped for twenty-five minutes which showed a rather large quantity of urobilin in the

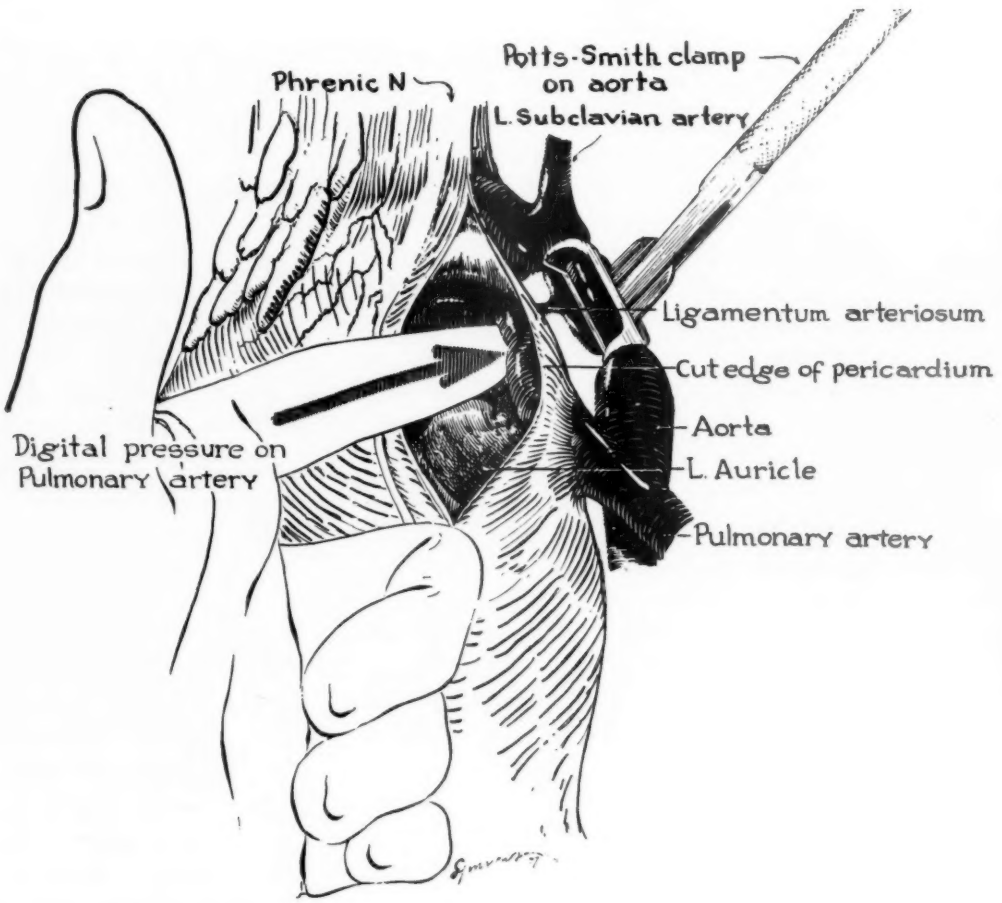

Fig. 1.—Technique for excision of ligamentum arteriosum in the dog with the use of the Potts-Smith clamp.

urine postoperatively. He interpreted this as a sign of impaired liver function due to the lengthy arterial anemia. Because of these complications it was felt wisest to avoid the use of the aortic clamps. The clamp described by Potts, Smith, and Gibson[19] for direct aorta-pulmonary artery anastomosis seemed ideally suited to our purpose, for it completely occludes the circulation through the ductus from its aortic end and does not impede free aortic flow.

A plan for the control of the components of the shunt was set up which consisted of (a) pericardiotomy with digital pressure on the left pulmonary artery and (b) a Potts-Smith clamp on the aorta. Excision of the ligamentum

arteriosum was performed in four dogs. On the basis of this experience, a modification of the Potts-Smith clamp was constructed which has been successfully used in a clinical case.

EXCISION OF THE LIGAMENTUM ARTERIOSUM IN THE EXPERIMENTAL ANIMAL

Through a left fourth interspace incision, the chest was opened and the mediastinal pleura incised posterior to the vagus nerve. The vagus and recurrent laryngeal nerves were freed and a rubber band placed around them for retraction. The aorta was mobilized close to the origin of the left subclavian artery, both anteriorly and posteriorly, and was surrounded with a rubber tube. The aorta below the ligamentum arteriosum was then surrounded by another rubber tube. The space between the aorta and pulmonary artery was opened up by blunt dissection with a curved hemostat. The pericardium was then opened posterior to the phrenic nerve. The ligamentum arteriosum was freed by following the line of cleavage of the recurrent laryngeal nerve. A suture was then

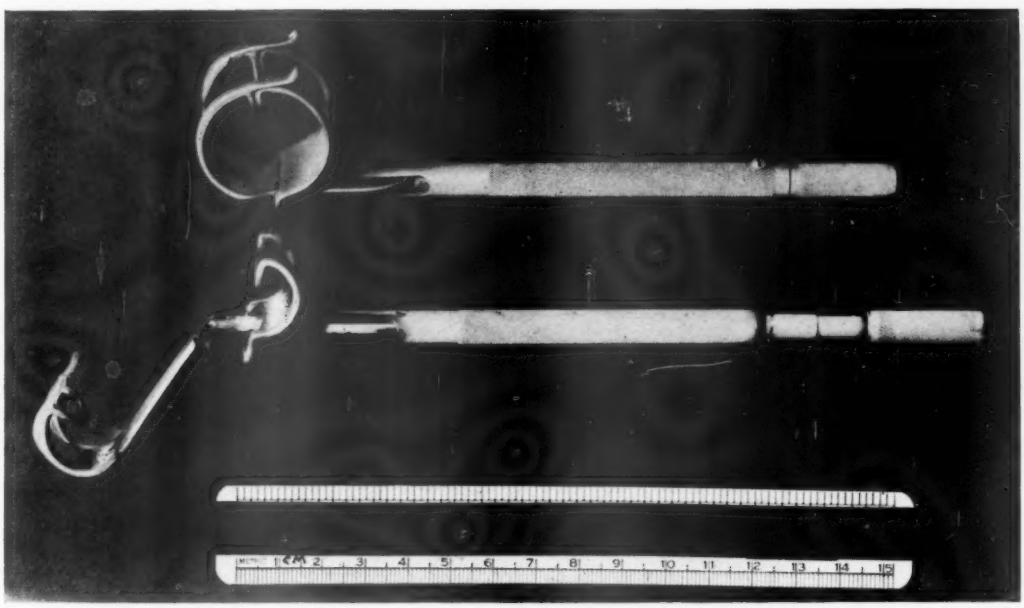

Fig. 2.—Modification of Potts-Smith clamp for occlusion of the origin of a patent ductus arteriosus.

passed about the ligamentum arteriosum and included portions of the wall of the pulmonary artery. At all times good control of the blood flow in the pulmonary end of the ductus arteriosus could be had by digital pressure on the left pulmonary artery through the pericardiotomy incision. With the use of the previously placed rubber tubes for traction, the Potts-Smith clamp was placed around the aorta so as to isolate the aortic origin of the ductus when the clamp was closed (Fig. 1). The ligature on the pulmonary end of the ligamentum arteriosum was tied. The ligamentum arteriosum was then divided and the aortic portion of the ligamentum with a small portion of aortic wall excised. The aorta was rotated outward and the opening in the aorta closed with a

longitudinal running stitch. The clamp was then released. The pericardiotomy incision was partially closed with two interrupted cotton sutures. The chest was then closed in layers.

Certain difficulties were noted in the use of the Potts-Smith clamp. Because of the straight handle it was sometimes difficult to place the clamp without excessive traction on the aorta. Even though we had access to clamps of several different sizes, there was usually a discrepancy between the diameter of the clamp and that of the aorta. Best results were obtained with a clamp slightly

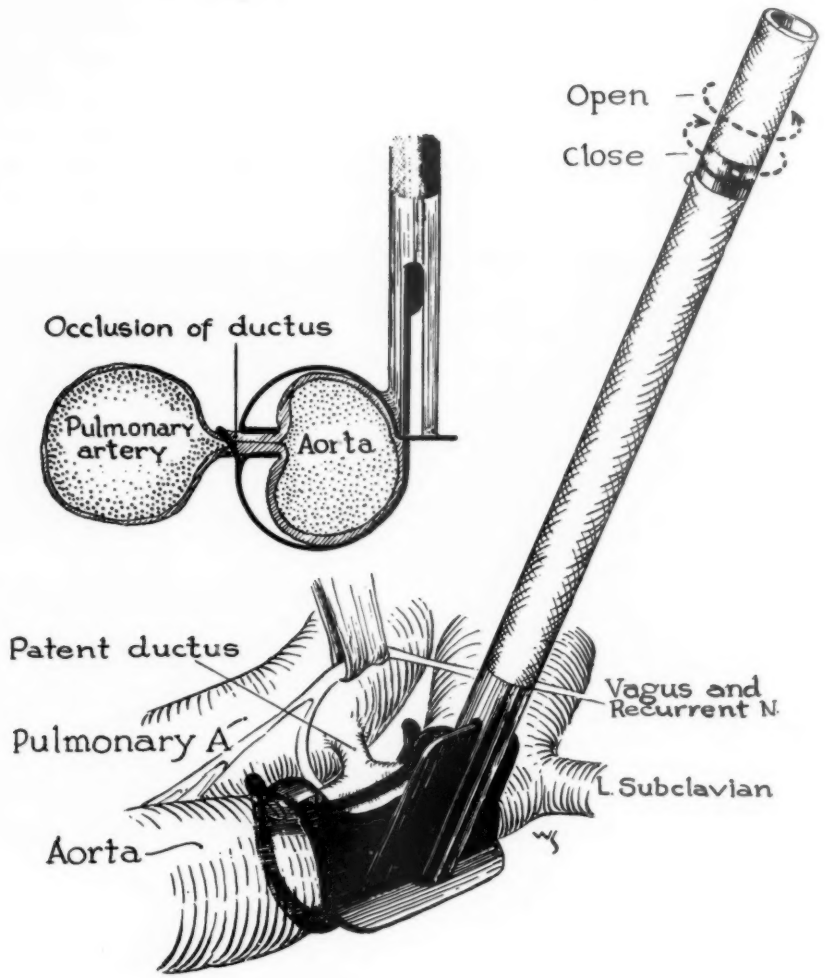

Fig. 3.—Special aorta clamp in place.

smaller than the vessel, but then there was a tendency for the aortic wall to bulge forward excessively and also for the back of the clamp to pinch the aortic wall. These difficulties were overcome by designing a clamp* which differed from the usual Potts-Smith in having (a) a swivel handle, (b) guides on the lower jaw to prevent bulging of the aorta, and (c) a smooth back which could not traumatize the aorta (see Fig. 2).

*We are grateful to Mr. Eliot D. Green of San Francisco for designing and constructing this clamp.

CLINICAL CASE

The patient was a 40-year-old woman with patent ductus arteriosus. Under curare, nitrous oxide, and oxygen anesthesia, the chest was entered through a posterior incision. The aorta was found to be greatly dilated at the origin of the ductus, being at least half again as large as it was just above or just below this point. The ductus came off approximately 2 cm. below the origin of the left subclavian artery and was approximately the same size as the subclavian artery. The pulmonary artery was dilated and a pronounced thrill could be felt, especially toward the medial side. The pericardium was incised for a distance of 6 cm. The aorta was encircled by a segment of rubber tubing below the ductus and another just above the origin of the left subclavian artery. By means of traction on these two rubber tubes, the aorta was raised from its bed and its posterior surface carefully freed. By means of sharp dissection the space just above the ductus was carefully opened so that it was possible to apply the special aorta clamp (see Fig. 3). The clamp was then screwed down to the point where it obliterated the thrill and was left in place for five minutes while venous pressure readings were taken. The pulse slowed from 80 down to 60, but the venous pressure did not rise. A braided silk ligature was passed above the ductus, being kept anterior to the recurrent laryngeal nerve, but no effort was made to dissect the loose tissue from about the pulmonary end of the ductus. After the clamp was screwed down, the ligature was tied as close as possible to the pulmonary artery. The ductus arteriosus was then divided with a knife close to the aorta. The pulmonary end of the ductus distal to the ligature was closed with a continuous over-and-over stitch. The aorta was then rotated outward and the opening in the aorta closed with a longitudinal continuous over-and-over stitch of 00000 Deknatel suture. A second running suture was then inserted. On removal of the clamp, only minimal bleeding occurred and there was only a slight indentation of the aorta in this region. The opening in the pericardium was closed with interrupted stitches of No. 40 cotton, the parietal pleura over the aorta being sutured in a similar manner. The chest was closed by layers. The patient recovered completely.

DISCUSSION

At the turn of the century, Matas[20] stressed the importance of prophylactic hemostasis in approaching an arteriovenous fistula. This prophylactic hemostasis is particularly important in the older age group of patients with patent ductus arteriosus in whom the ductus is friable and in those in whom there is an inflammatory endarteritis. The modified Potts-Smith clamp permits complete control of the aortic end of the ductus arteriosus without interfering with free aortic blood flow. Through the pericardiotomy incision the left pulmonary artery and the pulmonary end of the ductus are controlled. This pericardiotomy incision also facilitates exposure of the ductus.[7, 16, 21]

In a patient with infection, in whom Crafoord[14] had divided and sutured the ductus, a fistula formed between the aorta and pulmonary artery, and he suggested that excision of the diseased walls of the aorta and pulmonary artery would prevent this mishap. With the technique here described, it is possible to excise the patent ductus with a portion of the wall of the aorta and pulmonary artery.

Shapiro,[10] Crafoord,[4] and Wangensteen[7] have all reported cases of direct arteriovenous fisula between the aorta and pulmonary artery. The present technique lends itself admirably to the surgical repair of this type of defect.

SUMMARY

A method of prophylactic hemostasis in the surgery of patent ductus arteriosus, by the use of a modified Potts-Smith clamp, is described.

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PREVENTION OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM BY ELECTRICAL STIMULATION OF LEG MUSCLES

V. L. TICHY, M.D., CLEVELAND, OHIO

(From the Department of Surgery, Western Reserve University School of Medicine and the Surgical Service of Crile Veterans Administration Hospital)

WILLIAM HARVEY, in 1628,[1] first noted that muscular action was important in returning blood from the extremities to the heart. In his words: "Blood easily concentrates toward the interior, as drops of water spilled on a table tend to run together, from such slight causes as cold, fear, or horror. It also tends to move from the tiny veins to the intermediate branches and then to the larger veins because of the movements of the extremities and the compression of the muscles." The importance of muscular action during and immediately after operation prompted this work.

Preventative measures have markedly increased the scope and safety of surgical procedures in recent years. Most prophylactic measures have to do with preparing patients for operation or avoiding complications of the immediate postoperative state, and the prevention of pulmonary embolism is within the latter category. The possibility of long-continued disabilities and of remote effects, which are sometimes more crippling than the disease or condition present before operation, should perhaps receive more attention. The prevention of thrombosis, not necessarily accompanied by embolism, is a problem of magnitude.

Renewed interest in pulmonary embolism and unsatisfactory results in the treatment of "varicose veins" and other congestive diseases of the lower extremities are two factors in pointing up the necessity for further investigation. The subject of the late sequelae of thrombosis of the leg veins has been repeatedly discussed by John Homans,[2] who also commented on the changes in such problems with recent methods of therapy. These late results often present much difficulty in treatment, permanent edema and functional difficulties of a minor degree being very common. Individuals with ulceration, pain, and swelling of the lower extremities can often be helped by proper treatment, but completely satisfactory solution of the problem can come only by prevention of the original thrombosis.

A few years ago, heroic operations were occasionally carried out to remove emboli from the pulmonary vessels. Recently, production of a better nutritional state, adjustment of water, salt, and protein balance, and the free use of blood and plasma have all assisted in reduction of postoperative venous thrombosis. This has been probably due to the maintenance of better circulation during operation and after, and the earlier return to normal reactions accompanied by muscle movements. Early ambulation is possible in more cases today because

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of such measures, and its use perhaps reduces the incidence of thrombosis and the spread of incipient thrombi. However, early ambulation does not mean immediate walking and sometimes it cannot be implemented within days or even weeks.

The sources of pulmonary emboli are generally conceded to be in the lower extremities in over 90 per cent of all cases, if one excludes from consideration those of purely cardiac origin. The writings of Hunter and his associates[3] cover the subject excellently in this respect and again emphasize earlier findings that venous thrombosis in the feet and legs is much more common than generally known.

Various prophylactic measures have been used recently with benefit. Ochsner and DeBakey,[4] among other measures, carry out wrapping of the lower extremities with elastic bandages. These must be applied with care to avoid harmful constrictions and are probably especially useful when patients have sizable varicosities. The Trendelenburg position is useful in preventing pooling of blood, but may not be advisable in some types of cases. Elevation of the lower extremities alone may lead to pelvic pooling, and we know that sometimes thrombosis begins in the prostatic and other pelvic veins. Allen and his associates[5] consider adequate measures of such importance that they advocate ligation of femoral veins as a prophylactic measure in selected cases. This does avoid long and deadly thrombi from the thighs and legs, and may, by forced utilization of pelvic anastomotic channels, cause speeding up of flow through pelvic veins with resulting benefit. However, we have felt that a defective venous circulation is thus produced with the possibility of deleterious late effects. The prophylactic use of anticoagulants[6-11] undoubtedly reduces thrombosis but introduces the hazards of hemorrhage if used in adequate dosage. If anticoagulant use is delayed, some degree of thrombosis may occur. If formation of incipient thrombi were to be avoided, anticoagulants would be necessary during operation, which is obviously impractical as a general rule. Early active motion is desirable and universally accepted, but methods requiring active cooperation on the part of the patient cannot be instituted early enough for complete protection, especially in the presence of serious illness or after extensive operations. In the treatment of patients in whom thrombosis has already taken place, we have used the anticoagulant method with satisfaction thus far.

During operation and for some time after, the patient's leg muscles are paralyzed by general or spinal anesthesia, and the blood pressure is often lowered. In extreme cases the circulation may be markedly slowed. After operation, the very sick patient moves his muscles little for a day or even several days, and during this time the legs and feet are sometimes immobilized with firm bed coverings. This is also too frequently true of the very ill medical patient, with cardiac or other diseases.[12] During this time, the patient's legs press upon a firm operating table or mattress and can often be seen to assume a triangular cross section, especially in undernourished individuals with soft muscles. Under these conditions, not only are the veins compressed, but trauma occurs, setting up ideal conditions for thrombosis. One need only to observe a

patient operated upon under local anesthesia, using light sedation, to realize that the legs soon become very uncomfortable. Heavy sedation postoperatively, desperate illness, or pain elsewhere are the only things that prevent patients from moving about considerably and changing position to avoid such trauma and the accompanying pain. The trauma may be direct to all the tissues, including the veins, and aggravated by interference with circulation in capillaries, venules, and veins. It is pertinent that only rarely are the anterior leg veins the seat of the original thrombosis. Likewise, forearm and arm veins are seldom the seat of thrombi leading to embolism, except in cases of obstructive lesions. That trauma alone does not lead to massive clot formation is indicated by the relative freedom from this complication in arm veins used for intravenous medication. Here, despite puncture and at times irritating solutions even leading to inflammation, massive thrombosis is relatively infrequent. Thus it seems that a combination of trauma and stasis is necessary for the formation of thrombi and their growth. A clot which is present only in the leg veins may remain trapped there by the numerous branches and connections between the veins, but when it extends into the popliteal and femoral veins, it can be broken loose easily by bending of the knee and the squeezing action of the muscles. The more comprehensive discussions and studies of etiology by Karsner,[13] Hunter and his associates,[3] Frykholm,[14] Smith and Allen,[15] O'Neill,[16] and others generally support the need for early prophylaxis.

In view of these facts, it was felt that the methods in use, while remarkably lowering mortality and perhaps morbidity, were still inadequate chiefly because preventative measures were not instituted soon enough. It seemed that a stimulation of the blood flow immediately after operation and even during prolonged operations would reduce the incidence of leg vessel thrombosis. A method not requiring cooperation of the patient was needed and it seemed that electrical stimulation could produce the desired result. It could be applied with no inconvenience to the patient, could be used intermittently and even during anesthesia or sleep. Accordingly, I saw Dr. H. T. Zankel, of the Department of Physical Medicine Rehabilitation, who suggested that a sinusoidal type of current would give a good reaction without undue disturbance of the patient. A stimulus given to the calf muscles, thirty times a minute for one-half hour, with one-half hour rest period, and continued for at least twenty-four hours was decided upon, and we have had no reason to change this during the course of the experiment since early in January, 1947. In a few instances treatment has been prolonged for two days. Some patients had a short massage of the leg muscles while still on the operating table, and this should be done to all. No attempt was made to determine unusual clotting tendencies before or after operation, though this factor is of importance, as shown by the work of de Takats.[17] Some patients would probably have profited by a continuation of modified treatment, with muscle stimulation carried out four or five times a day. Stimulation sufficient to contract the calf muscles so as to move the foot slightly was the objective and thigh muscle stimulation was not attempted during this study.

RESULTS

In order to obtain directly comparable statistics, this method should be carried on to include about 20,000 patients, one-half treated and one-half untreated, but this would obviously prolong the experiment too greatly before rendering a report, if good major cases were chosen. The results after treating over 800 are encouraging despite the fact that the machines were never used more than two days postoperatively, and no other unusual nursing or medical care was given.

There was no complaint on the part of the patients, except for occasional slight burning sensations which could usually be eliminated by readjustment of the electrodes and current. On two known occasions, however, the current was apparently too intense and caused subsequent tenderness. This is of special importance in patients with insufficient arterial circulation, such as those with arteriosclerosis obliterans. Here, especially when narcotics are used, close supervision of the technicians is necessary. No other deleterious side effects were noted. The contractions of the calf muscles generally caused slight foot movements, but these did not interfere with sleep. Some patients volunteered the information that it gave them the sensation of having taken a walk, and we feel that the mild exercise provided is beneficial.

During the first three months the apparatus was used mostly on patients who had herniorrhaphy, excision of pilonidal sinus, anal fistulectomy, and even hemorrhoidectomy. For the last fifteen months most of the extensive cases on the general surgical service have been treated, choice being based on the extent and seriousness of the operation whenever possible. A large proportion of the patients was in the older age group. Patients with venous ligation of any type were not included in the statistical table for obvious reasons. Those with hemorrhoidectomies and similar procedures treated in the last six months were not included because it was felt that such minor procedures are less likely to produce leg thrombosis and therefore would weigh the results too favorably.

The six cases of venous thrombosis occurring despite this treatment are worthy of some discussion.

CASE REPORTS

CASE 1.—This 60-year-old man had hemiplegia five years previously with marked residuals. He was admitted with marked anemia, weakness, and loss of appetite, and was found to have a carcinoma of the cecum and ascending colon. Following multiple transfusions he had a right colectomy with transverse ileocolostomy. The leg muscles were stimulated for two days. One week later he was allowed up and eviscerated, requiring secondary closure, and was again treated by leg stimulation for one day. Three days later he had bilateral bronchopneumonia. Eighteen days after the original operation, and eleven days after secondary closure, he developed a superficial (saphenous vein) acute thrombophlebitis, which gradually involved the great saphenous system to the groin, with possible deep extension of some degree. It subsided without incident on anticoagulant therapy, which was maintained seven days. Five days after discontinuing Dicumarol, he showed evidence of intra-abdominal hemorrhage. Hemoglobin was 28 per cent, red blood cells 1.4 million, and prothrombin time was 20 per cent of normal. Treatment was with vitamin K and 5,500 c.c. of blood. At the time of discharge there was slight residual swelling of the leg.

CASE 2.—This 52-year-old man had had urinary bladder symptoms since 1943. There was a diagnosis, by biopsy, of transitional carcinoma in 1945. In January, 1946, he had x-ray

therapy and in February, 1947, he was given a second course together with radium treatment. He finally became severely constipated and was admitted in July, 1947. Examination showed induration of the abdominal wall and groins, and skin changes due to irradiation were present. A large mass was palpable through the rectum, chiefly on the left side. On August 5, a transverse colostomy was done because of partial obstruction, and leg muscles were stimulated for twenty-four hours. There was phlebitis with thrombosis of the arm veins during the immediate postoperative course, but none in the legs. On August 25, twenty days after colostomy, thrombophlebitis was first found affecting the saphenous veins. Later the calf veins were involved. Recovery from the thromobphlebitis was uneventful, but the patient subsequently died with bronchopneumonia.

CASE 3.—Exploration was done on an elderly man and he was found to have an inoperable carcinoma of the stomach. Peritoneal implants were found in the pelvis though without any large mass. He was treated with leg stimulation for only one day, and it was not started until three hours after operation. There was postoperative gastric dilatation and ilius, and the fourth day after operation there was a rapidly developing thrombophlebitis of the entire left lower extremity, with little discomfort. During the next two days, edema involved the scrotum and inguinal regions, but later subsided. He had no specific treatment for the thrombosis except elevation, but the swelling subsided to a considerable extent.

In none of these three cases did the thrombosis originate within the calf veins, the usual site of origin of the silent type of thrombosis or phlebothrombosis. In the first, it is interesting that despite all the patient's troubles, thrombosis did not occur until well along the course, after a bout of pneumonia. Perhaps he needed circulatory stimulation during the pneumonia more than at other times. The second was really a case of terminal care. The fact that thrombosis in the legs was avoided for so long was remarkable in view of the thrombosis in the arms, and the pelvic tumor mass. It is felt that the treatment delayed leg vein thrombosis, which occurred almost three weeks after the exploration. The course indicates that he was the type with a tendency to thrombosis. Only in Case 3 did the complication occur soon after operation, and here it probably was primarily pelvic vein thrombosis. This man's blood pressure was subnormal during the first two days and treatment should have been started sooner and prolonged for at least another day. The diagnosis, no doubt, tended to preclude vigorous therapy.

CASE 4.—This man was 52 years old, with diabetes and arteriosclerotic gangrene of the left foot, necessitating a mid-thigh amputation on Oct. 8, 1947. After a good recovery, right lumbar sympathectomy was done on November 5. One day after operation, he complained of some soreness of the right calf, and the following day a superficial vein was found thrombosed. This was treated with anticoagulants and he did not develop any swelling or extension of the process. The leg appears normal at present.

CASE 5.—A man of 25 years, with perforated gastric ulcer, had the perforation sutured under general anesthesia. Four days after operation, despite a one-day treatment by leg stimulation, he developed a typical thrombophlebitis of the right calf, with extension upward to the thigh. He responded well to anticoagulant therapy.

CASE 6.—This 60-year-old man had a large right direct inguinal hernia. There was some perianal eczema. The heart was normal in size, there was a systolic murmur, and the blood pressure was 140/100. There was also mild emphysema. Right inguinal herniorrhaphy required considerable time, the bladder presenting in the sac. In the repair, Cooper's ligament was utilized. Temperature on the fourth day reached 102° F. and calf tenderness was present on the right. He was treated with anticoagulants, but also developed left calf ten-

derness with a positive Homans sign the following day. However, temperature returned to normal on the sixth day and remained so thereafter. No demonstrable swelling occurred. The patient had received forty-eight hour treatment, but it was not started for some time after return from the operating room.

These last three patients had involvement of calf veins, though the phlebitis in Case 4 was quite superficial. In this patient the treatment was probably too vigorous. This was a dangerous type of case, with recent thrombosis of arteries of the other leg, and an impaired arterial circulation in the leg under treatment.

A study of Table I indicates that with the exception of the first two classes, we have chosen to treat cases of truly major caliber. Among those patients with acute appendicitis were some who traveled considerable distances to reach the hospital. A large proportion of the patients was in the older age groups, as indicated by the types of operations necessary; even in the hernia group 46.4 per cent of them were over 40 years of age. Many of the patients had been hospitalized elsewhere previously. To counterbalance this, the preoperative and postoperative care was of the highest order and intravenous therapy was used fully as required. Operations were performed by a number of surgeons, a considerable portion being done by the resident staff.

TABLE I

TYPE OF CASES	TOTAL	WITH THROMBOSIS
Anorectal, including hemorrhoidectomy	76	
Pilonidal sinus, fistula, perirectal abscess	66	
Hernia, including bilateral, femoral, and many with Cooper ligament type of repair	259	1
Ventral hernia	13	
Miscellaneous extensive procedures, including jaw resections, grafts, tumors	70	
Appendectomies, chiefly emergency	71	
Cholecystectomies, duct explorations	42	
Major gastric, including resection, gastroenterostomy plus vagotomy	42	1
Miscellaneous abdominal, including resection of tumor, exploration with colostomy, abscess	42	2
Intestinal resections	17	1
Major thoracic, chiefly lobectomies	24	
Vagotomies	23	
Sympathectomy, dorsal or lumbar	37	1
Thigh amputations	10	
Total	792	6
With thrombosis .76 per cent		
Embolism 0		

Our files are not extensive enough to furnish figures for comparison, but based on general experience with operations of like nature, we might conservatively have expected an incidence of thrombosis of 4 or 5 per cent. Despite the fact that most of our serious cases were treated by stimulation, there were some patients who, because of lack of apparatus or other considerations, were not included. Among these were four patients who had pulmonary embolism, one of them dying. This is pertinent, in that there was not one case of embolism in our treated series. While it should be noted here that four of our six cases

of thrombosis were treated with anticoagulants after the diagnosis was made, the evidence indicates that prevention of incipient thrombosis has led to decrease in the extensive type of thrombi that cause embolism. This is a desirable, important corollary to our chief aim, which is the reduction of morbidity from thrombosis of lower extremity veins in general.

DISCUSSION

Modifications of this treatment will undoubtedly be made in the future, and there is no reason why treatment should have been limited to the immediate postoperative period other than definite control for purposes of accurate study. Treatments were given under the supervision of the physiotherapy department by ward attendants. It is best when ward surgeons designate specifically the amount of treatment and also make occasional observations on the efficacy of the stimulation. One factor of importance is the beginning of the treatment as soon as the patient is returned to the ward.

There are no absolute contraindications to use of this therapy, but in patients with impaired arterial circulation, caution must be exercised. Possible difficulties in conditions such as arteriosclerosis obliterans or Buerger's disease include injury to muscles by local overheating or forced exercise beyond the fatigue point.

While our series is not large,* results thus far indicate that one can expect a marked drop in the incidence of leg vein thrombosis by electrically stimulating the leg muscles during the time that circulation is impaired, in patients undergoing operation. Most important is the fact that this is accomplished with few deleterious side effects and with a minimum of expert care. The effectiveness of such treatment given only a few times a day is still to be determined. It has the further advantages of mildly exercising the muscles regularly without interfering in any way with other treatment and may thus be useful in general medical diseases and in the treatment of victims of fractures.

A project such as this requires the cooperation of many workers, and the writer gratefully acknowledges that given by the entire Surgical Staff and the staff of the Department of Physical Medicine Rehabilitation of Crile Veterans Hospital.

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A COMPARISON OF SYMPATHOLYTIC EFFECTS OF PRISCOL,* ETAMON,† AND DIBENAMINE‡ IN DOGS WITH RESULTS OF ACTUAL SYMPATHECTOMY

F. A. Marzoni, M.D., M. J. Reardon, M.D., J. P. Hendrix, M.D., and K. S. Grimson, M.D., Durham, N. C.

(From the Departments of Surgery and Medicine, Duke University School of Medicine)

POSSIBLE clinical use for sympatholytic drugs has been established by surgery. Removal of upper dorsal or lumbar portions of the sympathetic nervous system aids treatment of certain patients with peripheral vascular disease.[1] Sympathetic denervation of the splanchnic area, lower trunk, and occasionally legs (Smithwick[2]) or denervation of most or all of the body including thoracic as well as splanchnic visceral areas and head, arms, and upper trunk together with part or all of the lower trunk and legs[3] has aided treatment of many patients with hypertension.

Potential use for sympatholytic drugs as aids to diagnosis or prognosis also has been established by surgical methods. Temporary block of lumbar or upper dorsal sympathetic ganglia by injection of a local anesthetic and block of preganglionic fibers to the legs with spinal anesthetic have been recommended as methods of determining indications for sympathectomy in patients with peripheral vascular disease. Also, high spinal anesthesia has been suggested as a method of determining advisability of sympathectomy for hypertension.

Either local block or spinal anesthesia may produce changes of circulation simulating immediate results of sympathectomy but may fail to predict lasting results of chronic denervation which would be effected by operation. Immediate changes in circulation might be estimated by drugs capable of duplicating effects of sympathectomy. Also, effects of chronic denervation and results of actual sympathectomy might be predicted by use of such drugs if therapeutic effects could be maintained during treatment lasting several days or longer. Finally a safe, sympatholytic drug effective during continuous treatment might replace sympathectomy in certain patients or aid in the treatment of others in whom operation is contraindicated.

Most of the newly developed sympathetic blocking drugs are first adrenolytic, small doses blocking the blood pressure-elevating action of epinephrine. In one field of surgery, particularly, this would be important. Diagnosis of pheochromocytoma or paraganglioma is often uncertain. When diagnosis is confirmed by exploration, removal of the tumor is associated with risk of shock from epinephrine intoxication. Preoperative preparation by an adrenolytic drug might aid diagnosis and possibly treatment of these tumors.

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Adrenolytic and sympatholytic drugs have been known for many years and many new preparations have been and are being developed. Among the earlier drugs ergotoxine, the Fourneau compound F 933,* and yohimbine are described as primarily and predominantly adrenolytic. Ergotamine tartrate and F 883 are said to be predominantly sympatholytic. Investigation of these compounds gave promising experimental results, but usually toxicity or undesirable side effects discouraged use clinically.

Three new drugs have currently received clinical trial and have been judged reasonably safe. These are Priscol (2-Benzyl-4, 5 Imidazoline hydrochloride), Etamon (tetraethylammonium chloride or bromide) and Dibenamine (dibenzyl beta-chloroethyl amine hydrochloride). Literature describing special properties of these drugs has been reviewed by Ahlquist and associates,[4] Acheson and Moe,[5] and Nickerson and Goodman,[6] respectively, as well as by many others. Therefore, only a brief summary of currently accepted properties will be presented.

In 1939 blood pressure-depressing action of Priscol was described by Hartmann and Isler.[7] Meier and Mueller[8] noted dilatation of vessels of mucosa and skin. Hatt,[9] using the Starling heart-lung preparation, found damaging doses of Priscol are 100 times greater than those used to reduce blood pressure. Priscol evidently stimulates cardiac output and produces vasodilatation of coronary vessels. Adrenolytic action was noted by Meier and Mueller[8] and was clarified by Meyer[10] and Chess and Yonkman.[11] Cholinergic action on ileum of dogs was described by Yonkman, Hays, Cameron, Pellett and Hansen.[12] Ahlquist and Woodbury[13] observed that Priscol inhibits pressor and constrictor effects of sympathomimetic drugs but has little effect on depressor and dilator actions. Ahlquist, Huggins, and Woodbury,[14] reported that Priscol has complex pharmacologic actions which vary in different species. For example, the drug produces sympathomimetic and adrenolytic as well as acetylcholine-like effects.

Blocking action of Priscol apparently occurs at end organs of the adrenergic components of the sympathetic nervous system. Evidently, only excitatory pathways are blocked, and the inhibitory pathways remaining are relatively unaffected. Priscol is effective when given orally, intramuscularly, or intravenously.

The literature describing clinical use of Priscol for patients with peripheral vascular disease and hypertension has been reviewed in a separate report.[15]

Properties and site of action of tetraethylammonium chloride or bromide have been studied extensively by Acheson, Moe, and their associates,[5] Berry, Campbell, Lyons, Moe, and Sutler,[16] and many others. Acheson and Moe[5] demonstrated that the tetraethylammonium ion exerts its effect by blocking efferent pathways in autonomic ganglia. Acheson and Pereira[17] suggested that action within the ganglion is similar to the ganglionic blocking action of curare. The tetraethylammonium ion does not block pressor action of epinephrine. It is effective when given intramuscularly or intravenously but not when given orally.

Properties of Dibenamine have been reported chiefly by Nickerson and Goodman.[6] They demonstrated that it is an effective adrenolytic and sympatholytic agent. Mode and site of action are thought to be similar to that of

*Since this manuscript was written, Goldenberg, M., Snyder, C. H., and Aranow, H., J.A.M.A. 135: 971-976, 1947, have reported clinical use of F 933 as a diagnostic agent in adrenal tumors.

Priscol, that is, block of end receptors of the sympathetic nervous system. It is of interest that effects of this drug may persist twenty-four hours or longer. Recent reports of clinical trial have confirmed these properties but have indicated possible toxic effects in the central nervous system, even with relatively small dosage.[18] Dibenamine usually has been given intravenously since necrosis results with other parenteral routes and it may not be well tolerated by mouth. Because of desirability of developing sympatholytic and/or adrenolytic agents for possible clinical use, this experimental study of drug effects was undertaken in dogs. A comparison of the effects of each of the three new drugs was desired. Experiments were designed to test reflexes known to be abolished in dogs by total sympathectomy or by lumbar ganglionectomy.

Complete sympathectomy in dogs abolishes the carotid sinus pressor reflex, elevation of blood pressure with stimulation of the central end of divided vagus nerves, and the pressor response to anoxia.[1, 19] It also lowers mean systolic blood pressure to values around 80 to 100 mm. Hg. Complete sympathectomy neither abolishes nor increases pressor responses to epinephrine. Lumbar sympathectomy abolishes active reflex changes of peripheral resistance as judged by the Nolf three-way cannula methods.[20]

Experiments were therefore designed to compare effects of Priscol, Etamon, and Dibenamine with these effects of sympathectomy. In addition, experiments were designed to test action of epinephrine and other drugs. Preliminary abstracts have been presented.[21, 22, 23, 24]

METHOD

Healthy dogs weighing 10 to 17 kilograms were used in all experiments. Each was anesthetized using chloralose 0.1 Gm. per kilogram administered intravenously. The trachea was isolated through a midline incision in the neck and a cannula inserted. Carotid arteries on each side were identified. Vagus nerves were dissected free and divided. Next a unilateral lumbar sympathectomy was performed through a midline transabdominal approach. The femoral artery of each leg was exposed and divided one inch below the inguinal ligament. Systemic arterial blood pressure was recorded using a mercury manometer attached to a cannula in the proximal end of the divided artery of the nonsympathectomized extremity. Mercury manometers were also attached to cannulas in the distal ends of each of the divided femoral arteries to yield an indirect measurement of peripheral resistance as described by Nolf. Respiratory activity was recorded by means of a pneumograph connected with a tambour. All measurements were recorded continuously using a kymograph. Hemostasis was carefully maintained throughout each experiment.

Since a comparative assay of action of the three drugs was desired, a series of tests of vasomotor reflexes and responses to epinephrine was planned and executed during each experiment. Four or more experiments were conducted with each drug using a freshly prepared animal each time and repeating a series of tests several times in each animal. Tests included bilateral occlusion of the common carotid arteries using bulldog arterial clamps and maintaining occlusion one minute, intravenous injection of 0.03 mg. of epinephrine, stimulation of

proximal segments of a divided vagus by a faradic current and anoxia or asphyxia. Other tests occasionally employed were stimulation of the distal end of the right vagus nerve and administration of pituitrin or prostigmine. During each test changes of pulse, systemic blood pressure, peripheral femoral blood pressure, and respiration were noted.

This series of tests was performed before and after administration of each of the three drugs. Priscol, Etamon, or Dibenamine were given in varying doses. When a small dose was used initially, progressively larger doses were injected and each was followed by repetition of tests. Large or consistently effective doses were administered by the end of each experiment.

EXPERIMENTAL RESULTS

Priscol

Blood Pressure and Pulse.—Priscol in amounts varying from 0.05 to 7 mg. per kilogram was given intravenously as an initial dose in six animals. No change of blood pressure was produced by 0.05 mg. per kilogram in one animal; 0.07 mg. per kilogram in two produced depression of mean systolic blood pressure from 100 mm. Hg to 70 and from 132 to 100; 0.6 mg. per kilogram was followed by a rise from 124 to 188 in one; 2.0 mg. per kilogram in another dog produced a rise from 160 to 230. Blood pressure remained elevated 8 to 16 minutes. The sixth dog given 7 mg. per kilogram responded with a temporary elevation followed by a gradual decline (Fig. 1). After intervals of approximately one-half hour, five of these dogs were again given Priscol intravenously. Subsequent injections varied in number from three to nine, individual doses varied in amounts from 0.37 to 9.0 mg. per kilogram, and total dose varied from 6.4 to 35 mg. per kilogram. Each subsequent injection produced decrease of blood pressure in three dogs. A one minute rise followed by decline occurred in one after 5 mg. per kilogram. The fifth dog which had a rise from 124 to 188 following the initial 0.6 mg. per kilogram also had similar rises after 1.2 and 3.6 mg. per kilogram. Subsequent injections of 6.0 and 9.0 mg. per kilogram, however, produced decreases of pressure. In all six animals a gradual decline of blood pressure started after the initial or the first subsequent injection of Priscol and continued throughout the experiment finally reaching shock levels below 70 mm. Hg. Also, in each of the six, pulse rate consistently increased following the initial dose and throughout subsequent injections remained 20 to 50 beats per minute faster than before Priscol.

Carotid Sinus Reflex.—Before Priscol, occlusion of both carotid arteries produced elevations of mean systolic blood pressures in six animals. Increases ranged between changes from 128 to 184 mm. Hg in one animal to 140 to 220 mm. Hg in another. After initial injection of 0.05 mg. of Priscol per kilogram in one animal and 0.07 mg. per kilogram in two others, reflexes and blood pressure were only slightly depressed. After 0.6 mg. per kilogram in one dog mean systolic blood pressure increased and the reflex was reversed, lowering being from 178 to 148. Subsequently following larger doses in this animal the reflex increased pressure. After 2.0 mg. per kilogram in another the reflex was not changed. Following the single dose of 7 mg. per kilogram in one animal reduc-

tion of mean blood pressure and finally block of the carotid sinus reflex occurred (Fig. 1). Four of the five dogs receiving subsequent injections decreased the reflex response to rises between 130 to 146 and 106 to 126 after 0.5 to 10 mg. per kilogram. Response was finally blocked after doses of 6 to 25 mg., following

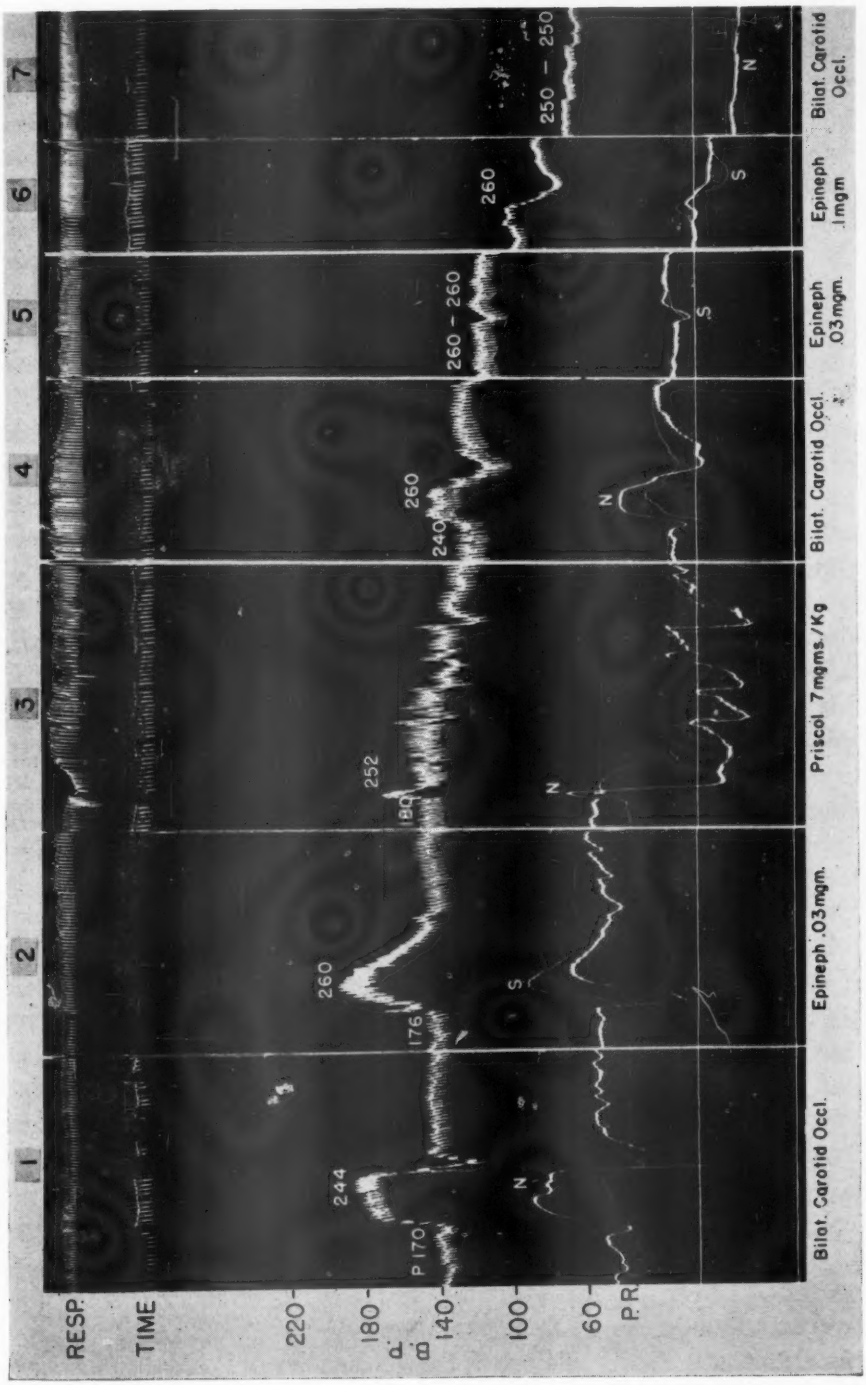

Fig. 1.—Effects of occlusion of both carotid arteries and of intravenous injection of .03 mg. of epinephrine upon respiration, mean systolic systemic blood pressure, and upon back pressure of a normally innervated limb (*N*) and of a sympathectomized limb (*S*) are shown in Panels 1 and 2. Administration of Priscol (7 mg. per kilogram, Panel 2) produced increase of pulse rate and gradual decrease of systemic blood pressure. A prompt and marked decrease of back pressure of the normal limb occurred, that of the sympathectomized limb declining more gradually. The four panels on the right demonstrate consecutively reduction of carotid sinus reflex, block of response to epinephrine, reversal of response to epinephrine, and finally complete block of response to carotid occlusion. Blood pressure gradually reduced during the experiment.

one to two hours of experimental study and after reduction of mean systolic blood pressure to levels ranging from 50 to 74 mm. Hg. Only one animal had complete block of the reflex at higher blood pressure levels. Mean systolic blood pressure, originally 130 mm. Hg in this dog, became 178 after 0.6 mg. per kilogram, 160 after addition of 1.2 mg. per kilogram, and 120 after another 3.6 mg. per kilogram. Carotid sinus reflex was blocked at all levels as also subsequently when increased dosage had decreased the blood pressure.

Epinephrine.—Before Priscol, 0.03 to 0.05 mg. of epinephrine administered intravenously to each of six dogs produced elevations of blood pressure ranging from 108 to 178 mm. Hg in one and from 156 to 250 in another, and increases of pulse rate ranging between 156 to 196 and 176 and 260. After initial doses of Priscol as low as 0.03 to 0.07 mg. per kilogram pressor responses to .03 and .05 mg. of epinephrine were reduced, a typical change being from 110 to 150 mm. Hg. After 1.8 to 11 mg. per kilogram of Priscol, doses of epinephrine varying from 0.01 to 0.1 mg. per animal usually effected reduction of blood pressure (epinephrinal reversal) and rarely an increase. When increase occurred it was less than 16 mm. Hg (Fig. 1). This response maintained whether or not mean systolic blood pressure had been reduced. Doses of epinephrine as high as 1 to 3 mg. per dog also produced moderate lowering or only slight increase of blood pressure. Heart rate was accelerated by Priscol almost as much as by epinephrine. Hence, epinephrine administered after Priscol caused little additional speeding of the heart. Examination of consecutive tests reveals that block or reversal of the usual pressor response to epinephrine occurred with doses of Priscol smaller than those required to produce reduction or block of carotid sinus and other reflexes. Also, when single effective doses of Priscol were given (Fig. 1) block of pressor response to epinephrine occurred sooner than block of reflexes.

Pituitrin and Prostigmine.—Ten and twenty units of Pituitrin, respectively, were given to two dogs whose blood pressure had been markedly reduced by Priscol. Pressure rose from 56 to 78 mm. Hg in one and from 22 to 94 mm. Hg in the other. Carotid sinus reflexes remained blocked. Pressure was not changed or reflexes restored by 0.5 mg. of Prostigmine.

Stimulation of the Central End of a Divided Vagus Nerve.—The central end of either divided vagus was stimulated before Priscol in four dogs using a tetanizing current. This produced marked elevation of blood pressure and increase in heart rate. After 1.9 to 11.4 mg. per kilogram of Priscol and after reduction of blood pressure, similar stimulation produced rises ranging between 48 and 102 and 72 and 132 mm. Hg. After 6.7 to 20.4 mg. per kilogram and after further reduction of blood pressure, elevation with central vagus stimulation was blocked.

Asphyxia.—At the termination of five of these experiments and after large doses of Priscol had been administered and marked reduction of blood pressure had occurred, tracheal cannulae were occluded, producing death by asphyxia. Blood pressure failed to rise in three animals, and rose only from 37 to 56 mm. Hg and from 80 to 100 mm. Hg in the remaining two.

Peripheral Resistance of Normal and Sympathectomized Hindlimbs Estimated by Nolf Method.—Throughout these tests back pressures from the distal

ends of divided femoral arteries were recorded by mercury manometers to estimate peripheral resistance. A separate manometer was used in the proximal end of one artery to record systemic blood pressure. Peripheral resistance was estimated by relating changes of back pressure in the normal and the sympathectomized limb to those of systemic blood pressure. Before Priscol, back pressure of the normally innervated limb altered rapidly and actively in response to reflexes, while that of the sympathectomized limb reflected changes of systemic blood pressure. Increases were usually less extensive than those of the normally innervated limb (Fig. 1). Also, before Priscol, back pressure of the normally innervated limb responded to 0.03 mg. of epinephrine usually first by decrease and then by increase; whereas, that of the sympathectomized limb promptly increased and reached levels somewhat exceeding the height reached by the normal limb.

Administration of initial doses of Priscol usually produced approximately equivalent changes in peripheral resistance of the normal and the sympathectomized limbs. Moderate differences, when they appeared, were in the direction of more prompt or extensive lowering of pressure in the normally innervated limb. Successive doses totaling 1.5 to 7 mg. per kilogram were required before reflex responses of normal and sympathectomized limbs became equal and passive.

Etamon

Blood Pressure and Pulse.—Etamon, 15 mg. per kilogram, administered intramuscularly in 3 dogs as an initial dose effected slow and moderate reduction of blood pressure and did not produce tachycardia. Etamon, 3 mg. per kilogram, administered intravenously as an initial dose in the fourth animal produced prompt reduction of mean systolic blood pressure from 102 to 54 mm. Hg and an increase of heart rate. Blood pressure recovered to 90 mm. Hg within five minutes. With one exception subsequent intravenous injections produced similar transient lowering of pressure followed by gradual but incomplete recovery, and subsequent intramuscular injections produced slow continued moderate reduction. The exception occurred in one animal following the initial administrations of Etamon. Consecutive intravenous injections of 5, 8, 8, 20, and 40 mg. per kilogram in this animal produced increases of pressure, the greatest being an increase from 110 to 190 after the 40 mg. per kilogram dose. Pulse rates increased during these pressor responses and then again slowed. A typical increase was from 132 to 184. The 40 mg. dose was followed by respiratory failure and death.

Carotid Sinus Reflex.—Before Etamon, occlusion of both carotid arteries produced elevations of blood pressure ranging between 106 to 140 and 130 to 180 mm. Hg. After initial doses of 15 mg. per kilogram intramuscularly in three dogs responses during one-half hour were reduced being between 60 to 80 and 110 to 128 mm. Hg. After an initial dose of 3 mg. per kilogram intravenously the reflex was blocked within three minutes. In all animals after the next injection occlusion of the carotid arteries produced no change of blood pressure (Fig. 2). Pressures were 52, 80, 82, and 84 mm. Hg at the time of the first complete block.

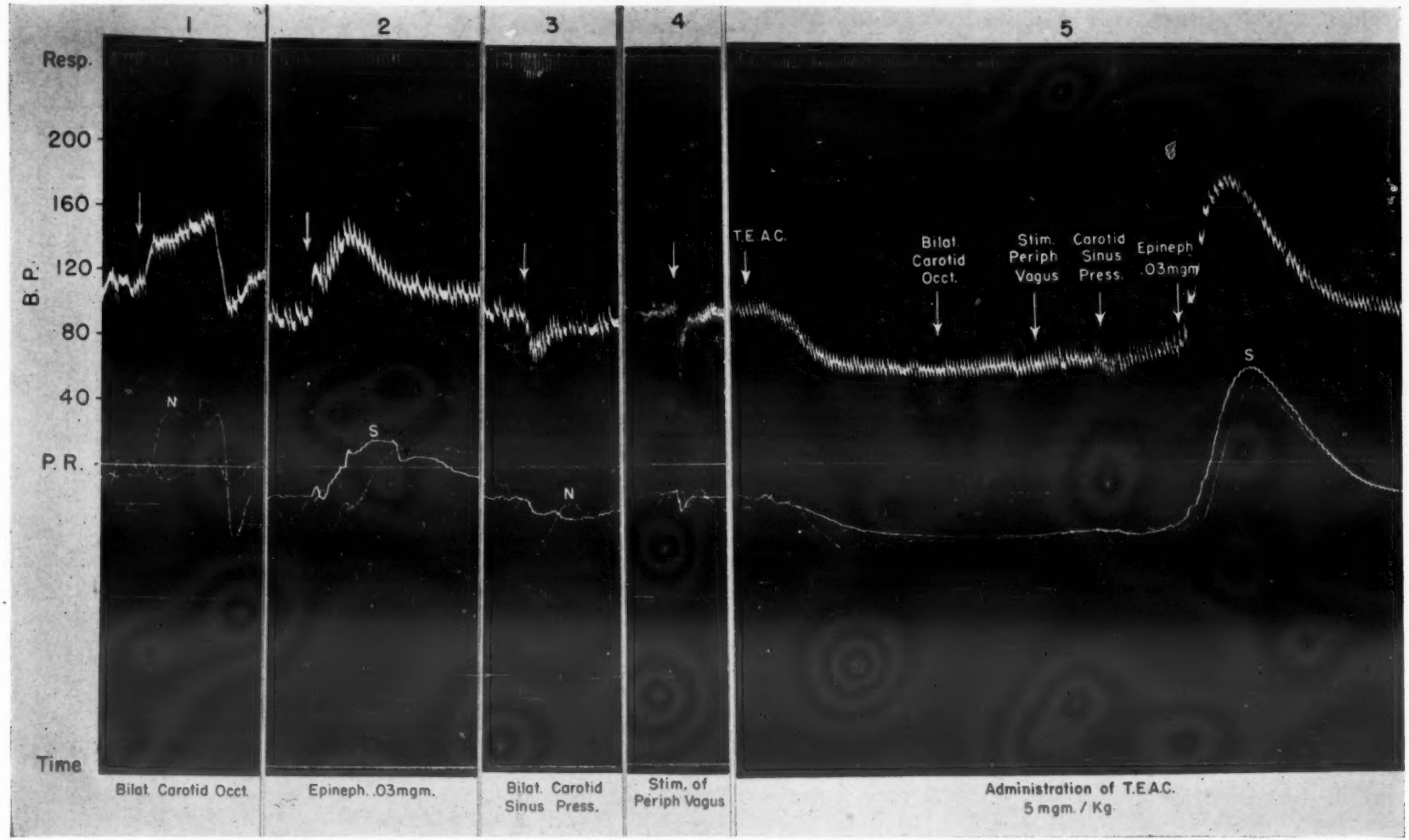

Fig. 2.—Control responses to occlusion of carotid arteries and injection of epinephrine are shown in Panels 1 and 2. Depressor response to pressure on the carotid sinus is shown in Panel 3. Stimulation of the peripheral end of a divided left vagus (Panel 4) produced cardiac slowing and lowering of blood pressure. Etamon (*T.E.A.C.*, Panel 5) promptly reduced blood pressure and blocked responses to carotid occlusion, vagus stimulation, and sinus pressure. It did not block pressor response to epinephrine, increase of blood pressure after Etamon (Panel 5) exceeding that before Etamon (Panel 2).

Epinephrine.—Before Etamon, .03 mg. of epinephrine in three dogs elevated blood pressure from 100 to 180, 128 to 172, and from 102 to 170 mm. Hg. The fourth dog required 0.1 mg. to elevate pressure from 124 to 186 mm. Hg. After initial and subsequent doses of Etamon the response to the same dose of epinephrine was equal in two animals, and definitely accentuated in two (Fig. 2) since the rise occurred from lower pressure levels, 64 to 154 and 60 to 182. mm. Hg.

Prostigmine.—Prostigmine in amounts of 0.5 mg. was administered intravenously to three dogs after cumulative total doses of Etamon ranging from 9 to 35 mg. per kilogram had effected reduction of blood pressure and block of carotid sinus reflex. Blood pressures rose after Prostigmine in the three animals from 62 to 82, 40 to 84, and 52 to 94 mm. Hg, respectively. Also, after this and subsequent larger doses of Prostigmine, carotid sinus reflexes became active although not equal to those before Etamon.

Stimulation of the Central End of a Divided Vagus Nerve.—Stimulation of the proximal end of one divided vagus nerve in three dogs before Etamon produced marked elevation of pressure and acceleration of heart rate. After initial and subsequent injections of Etamon, increase of blood pressure and increase of heart rate with stimulation were similar to that before the drug in two dogs and definitely blocked in one (Fig. 2).

Anoxia and Asphyxia.—Anoxia produced by spontaneous respiration of 7 per cent O_2 in 93 per cent N produced elevation of blood pressure before and after 15 mg. per kilogram of Etamon in one dog. Terminal asphyxia in another failed to elevate blood pressure.

Peripheral Resistance of Normal and Sympathectomized Hindlimbs Estimated by Nolf Method.—Back pressure or peripheral resistance of normal and sympathectomized hindlimbs was recorded throughout this series of tests in three dogs. Active and passive responses to reflexes were obtained before Etamon. Also, responses to epinephrine were diphasic in the normal leg and directly pressor in the sympathectomized limb. After effective doses of Etamon, carotid sinus reflexes were blocked and back pressure did not change during occlusion of the carotid arteries (Fig. 2). Stimulation of the central end of a divided vagus nerve usually elicited active and passive responses of back pressure lower, however, than those before the drug. Epinephrine after Etamon usually produced equal and active responses in the normally innervated limb and in the sympathectomized limb.

Stimulation of the Peripheral End of a Divided Vagus Nerve.—Before Etamon, stimulation of the peripheral end of the divided left vagus produced slowing of heart rate and reduction of blood pressure. After 21 to 25 mg. of Etamon this response was blocked, stimulation by tetanizing current producing no obvious effect.

Dibenamine

Blood Pressure and Pulse.—Initial doses of Dibenamine (5 mg. per kilogram) were administered intravenously to each of four dogs. This dose produced no change of blood pressure during fifteen minutes in one animal and a gradual decline in three (Fig. 3). Pulse rate changed little. Subsequent injec-

tion of 5 mg. per kilogram in each gradually hastened the decline of blood pressure and after one-half to one hour systemic blood pressure ranged from 40 to 64 mm. Hg.

Carotid Sinus Reflex.—Before Dibenamine, carotid sinus reflexes were active in four dogs, increases of blood pressure ranging between 106 to 140 and 128 to 204 mm. Hg. After initial injection of 5 mg. per kilogram reflexes were abolished in three animals at blood pressure levels of 60, 70, and 76 mm. Hg (Fig.

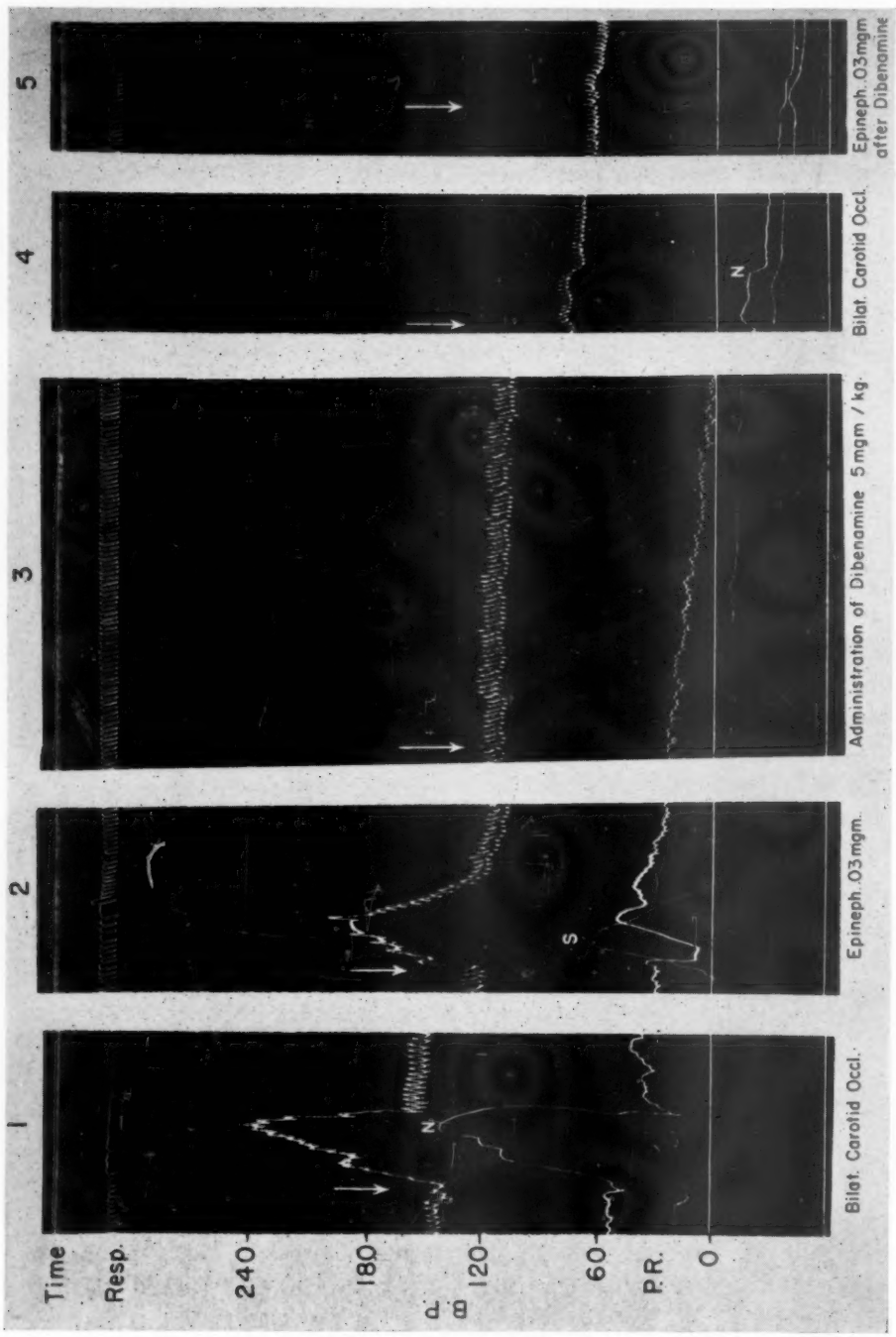

Fig. 3.—Control responses to bilateral occlusion of carotid arteries and injection of epinephrine are again shown on the left. Intravenous administration of Dibenamine (5 mg. per kilogram) effected slow gradual decline of systemic blood pressure and of back pressure in the normally innervated limb (Panel 3). One hour later (Panel 4) blood pressure was markedly reduced and carotid sinus reflex almost blocked. Pressor response to epinephrine (Panel 5) is blocked.

3). The fourth dog had a blood pressure of 96 after an initial 5 mg. per kilogram and it increased to 144 mm. Hg during carotid occlusion. After another 5 mg. per kilogram the response in this animal was 72 to 100 mm. Hg. Subsequently and without more of the drug, responses ceased.

Epinephrine.—Before Dibenamine, .03 mg. epinephrine produced elevations of blood pressure ranging between 120 to 192 and 104 to 212 mm. Hg. Soon after the initial dose of Dibenamine the pressor response to the same dose of epinephrine was blocked in one animal (Fig. 3), reduced in two (68 to 104 and 58 to 96 mm. Hg), and equal to that before Dibenamine in the fourth (110 to 176 mm. Hg). Following subsequent injections of Dibenamine, administration of epinephrine produced neither rise nor fall of systemic blood pressure.

Pituitrin and Prostigmine.—Twenty units of Pituitrin were administered intravenously to 3 dogs after total cumulative doses of Dibenamine of 10 to 20 mg. per kilogram and after reduction of blood pressure with block of reflexes. Blood pressures rose from 32 to 70, 52 to 146, and 82 to 130 mm. Hg, respectively, but reflexes were not restored. Prostigmine had no effect upon blood pressure or reflexes.

Stimulation of the Central End of a Divided Vagus Nerve.—Only two animals were tested after Dibenamine. Blood pressure had been reduced to 38 and 54 mm. Hg. Stimulation failed to increase pressure.

Asphyxia and Anoxia.—At the termination of each experiment the trachea was obstructed, producing death by asphyxia. Mean systolic blood pressure did not rise. Anoxia 7 per cent O_2 in 93 per cent N produced some elevation of blood pressure before Dibenamine in one animal and failed to produce elevation after the drug.

Peripheral Resistance of Normal and Sympathectomized Hindlimbs Estimated by Nolf Method.—Before Dibenamine, reflex changes of back pressure in the sympathectomized leg were passive and those of the normally innervated limb were active. After epinephrine, responses were direct and diphasic, respectively. Following initial and subsequent injections of Dibenamine, responses to reflexes in the normally innervated limb became passive and response to epinephrine was blocked, back pressure not changing in either the sympathectomized or the normally innervated leg.

DISCUSSION

Sympatholytic properties of Priscol, Etamon, and Dibenamine have in general been confirmed using techniques different from those described in the literature. Block of certain reflexes normally dependent upon the sympathetic nervous system does occur. Comparison of results of sympathetic block by drugs with previously reported results of total or lumbar sympathectomy in dogs indicates that the pharmacologic sympathectomy approaches effectiveness of actual sympathectomy. Back pressures of the normally innervated and the sympathectomized hindlimbs of a dog respond passively and equally to changes of systemic blood pressure produced by reflexes or drugs after effective doses of these three agents. Experiments have indicated, however, that pharmacologic blockade may vary from animal to animal and may fail to block strong pressor reflexes such as those produced by stimulation of the central end of a vagus nerve. Decrease or

block of the pressor response to this reflex usually occurs only after blood pressure has been reduced below shock levels. Block of the carotid sinus reflex occurs after less reduction of blood pressure.

Former experiments have indicated that reduction of blood pressure occurs during the first few months after total sympathectomy in dogs. This operation requires three operative procedures at intervals of several weeks following which blood pressures range from 80 to 100 mm. of mercury. Transection of the low cervical spinal cord in dogs effects among other things interruption of central vasomotor tone simulating an acute sympathectomy. Following cord section blood pressure is reduced to values around 70 to 80 mm. Either complete sympathectomy or division of the cord interrupts the carotid sinus reflex, the pressor response to stimulation of central end of the divided vagus, and increase of pressure with anoxia. The three drugs studied, in proper doses, produced comparable reduction of blood pressure and block of the carotid sinus reflex. Increased amounts of the drugs further reduced blood pressure to definite shock levels. Block of the pressor responses to anoxia and to stimulation of the central end of a divided vagus then occurred.

Experiments have indicated that two of the three drugs studied are similar in some respects. These, Priscol and Dibenamine, block or reverse the blood pressure-elevating action of epinephrine. They cause reduction of blood pressure which can be partially restored by pituitrin. The third drug, Etamon, is different in that is does not block epinephrine and blood pressure reduction is restored by prostigmine and not pituitrin. Prostigmine is apparently a good antidote in that restoration of blood pressure and recovery of autonomic reflexes occur.

Other differences between the three drugs will be discussed. Initial or subsequent injections of each usually reduced blood pressure. Occasionally, however, injections preduced transient elevations. Increases were most frequent after Priscol. Also, increase of pulse rate was more frequent and persistent after Priscol. Nevertheless, certain possible advantages of this drug were observed. Fall of pressure with Priscol occurred promptly with large doses and could be easily regulated by gradually increasing the total dose. The fall after effective doses of Dibenamine occurred only slowly and continued progressively lower for several hours. That after Etamon was abrupt and tended to be more transient. Also, although accurate measurements were not obtained, an increase of redness of the skin or occurrence of a peripheral cutaneous flush occurred after Priscol. This was obviously more intense than any changes effected by alteration of circulation through the skin after Dibenamine or Etamon. This effect together with block of the pressor response to epinephrine could be obtained without marked reduction of blood pressure by employing graduated doses of Priscol.

From the clinical point of view, therefore, Priscol seems to be the most easily administered and regulated of the three drugs. Our detailed clinical studies[15] have been limited to this preparation. It is of interest that 50 to 75 mg. given a patient every three or four hours produces marked increase of the peripheral or extremity circulation even though this dose range is not sufficient to block completely the response to adrenalin.[25] Also, this dose does not signifi-

cantly reduce systemic blood pressure-altering reflexes produced by cold or by breath holding.[15] Similarly it does not significantly reduce blood pressure in the supine or erect position. Since it evidently requires 50 to 75 mg. per patient to increase circulation of extremities, 125 to 175 mg. to produce adrenalin blockade, and 150 to 200 mg. to block reflexes and reduce blood pressure, the therapeutic effect desired can be selected by regulating the dose. Thus far, amounts of more than 75 mg. have been employed only for test purposes. Apparently, Priscol alone of the three drugs studied has in a low dose range this ability to produce peripheral vasodilatation, at a level below that necessary for adrenolysis or sympatholysis as judged by systemic arterial blood pressure reponses.

Dibenamine is similar to Priscol in its adrenolytic property and may be somewhat more effective as a systemic sympatholytic agent. Our clinical experience with this drug is limited. These experiments have indicated, however, that effective doses produce a gradual decline of blood pressure and that effects of the drug last many hours. Although prolonged action may be advantageous under certain circumstances, treatment of possible adverse reactions might be difficult in the absence of an effective antidote. Also, although there is some evidence that the drug may be given by mouth, administration clinically has usually been limited to the intravenous route.

Use of Etamon for disorders or diseases of the circulation is limited by accessory effects produced by its general ganglionic blocking action. Examples are loss of accommodation of the eye, decrease of cesssation of peristalsis throughout the alimentary tract, and alteration of function of the urinary bladder. Such parasympathetic blocking side effects do not occur after the two adrenolytic and sympatholytic drugs, with which different or characteristic side effects occur.[15] Etamon is not adrenolytic. Reduction of blood pressure occurs promptly after intravenous administration of amounts necessary to produce sympatholytic or parasympatholytic effects. Abrupt reduction of blood pressure may not be desirable, particularly if the cerebral or coronary arteries are markedly diseased.

Finally, these experiments would indicate that three useful drugs have been developed, each capable of simulating effects of sympathetic block or actual sympathectomy.

CONCLUSIONS

1. A study of the actions of Priscol, Dibenamine, and Etamon upon systemic and peripheral circulation by methods described has permitted comparison of effects of each drug with the others and with known effects of surgical sympathectomy.

2. A block of reflexes normally dependent upon the sympathetic nervous system approaching that effected by actual sympathectomy was achieved by each of these drugs.

3. Effects produced by any of the three drugs were occasionally irregular or variable, particularly with smaller doses.

4. Priscol and Dibenamine were found to be adrenolytic and sympatholytic agents. Pituitrin partially restored blood pressure reduced by these drugs.

5. Etamon behaved as a ganglionic blocking agent and was not adrenolytic. Prostigmine restored blood pressure reduced by this drug and also effectively restored reflexes which it has blocked.

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THE RELATIONSHIP OF GASTRIC ACIDITY TO GASTRIC AND EXTRAGASTRIC NEOPLASMS

SUAD NIAZI, M.B., S.B., D. STATE, M.D., A. E. TRELOAR, PH.D., AND O. H. WANGENSTEEN, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery and Biostatistics, University of Minnesota Medical School)

INTRODUCTION

THE association of achlorhydria and hypochlorhydria with gastric carcinoma is a fact that has been noted by many observers[1-6] and has been stressed in the diagnosis of gastric cancer. Little information, however, is available on the relationship betweeen gastric acidity and extragastric malignancies. This information is obviously of great importance for it would reveal whether consistently reduced gastric acidity is associated only with gastric malignancies or whether it is a manifestation of reduced function of the parietal cells in the glands of the gastric mucosa due to toxic systemic effects of any malignancy.

It was the purpose of this study to investigate the relationship between gastric acidity and extragastric malignancies.

REVIEW OF LITERATURE

In 1880, Fenwick[7] described marked atrophy of gastric mucosa in a group of patients with extragastric malignancies. In his group were included 16 patients with carcinoma of the breast, 2 with cancer of the rectum, and 1 with carcinoma of the bladder, penis, and groin (metastases); no gastric acid determinations were made, however. Ewald[8] in 1886 reported 1 patient with carcinoma of the duodenum 2 cm. below the pylorus who had gastric anacidity and gastric mucosal atrophy. Riegel[9] in 1886 observed lowered gastric acidity in a case of carcinoma of the esophagus. Moore, Alexander, Kelly, and Roaf[10] in 1905 found that there was reduced acidity or complete gastric anacidity in 17 cases of extragastric malignancies, and concluded that achlorhydria which is associated with gastric malignancy is not due to the local effect of tumor on the gastric mucosa because it was present in malignancies other than the stomach. Friedenwald and his co-workers[11, 12] investigated this problem twice, once in 1907 and again in 1927. In the later study, using the fractional meal as a gastric acid stimulant, they investigated 38 patients with various extragastric malignancies and found achlorhydria in 37 per cent and hypochlorhydria (less than 30° free acid) in and additional 18 per cent. This lowered gastric acidity persisted even after the removal of the malignancy by surgery. In 1939, Necheles and co-workers[13] showed experimentally that the gastric acidity in rabbits was not altered in the presence of diffuse extragastric carcinomatosis produced by the inoculation of the very malignant Brown-Pearce rabbit carcinoma.

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MATERIAL AND METHODS

All patients over the age of 50 years registering at the outpatient clinics of the University Hospitals for the first time were subjected to a gastric analysis employing three successive doses of 0.5 mg. of histamine, given hypodermically, as a stimulant to gastric secretion. Töpfer's reagent was used to test for free hydrochloric acid, and quantitative estimations were made using $\frac{N}{10}$ N_aOH and Töpfer's reagent as the indicator. In a number of instances the patients for one reason or another were not given the three conventional doses of histamine, but they did receive one or two injections of histamine, and these patients were included in our statistical data. Patients not receiving histamine were excluded from the study. Patients who had no free hydrochloric acid after histamine stimulation were considered to be achlorhydric. Those who had free hydrochloric acid following histamine stimulation were further subdivided into the following groups:

(a) Hypochlorhydria—maximum free hydrochloric acid not exceeding 29°.
(b) Normal acidity—free acid ranging between 30 and 49°.
(c) Hyperchlorhydria—free acid exceeding 50°.

The diagnosis of the tumors was based on microscopic examination of a section taken from a biopsy or from the tumor itself after excision.

OBSERVATIONS

In all, 1,315 patients over the age of 50 years had gastric analyses using histamine as the gastric acid stimulant. Of this group (Table I) 906 patients did not have tumors, either malignant or benign. Of the 409 patients with neoplasms, 337 had extragastric tumors and the remaining 72 had tumors of the stomach.

TABLE I. INCIDENCE OF NEOPLASTIC AND NON-NEOPLASTIC DISEASES IN PATIENTS EXAMINED

	NO.	PER CENT OF TOTAL
Neoplastic Diseases	409	31
I. Extragastric	337	25.4
(a) Malignant	244	18.3
(b) Benign	93	7.1
II. Gastric	72	5.6
(a) Carcinoma	57	4.5
(b) Benign	15	1.1
Non-neoplastic Diseases	906	69
Total	1315	100

Extragastric Tumors.—Table I indicates that of the 337 patients with extragastric tumors, 244 had malignant and 93 benign neoplasms.

Malignant Extragastric Neoplasms.—

Table II presents the types of neoplasms, the organs affected, and the varying degrees of gastric acidity found in the groups of malignant extragastric tumors. In the main, the number of tumors in each organ is small, ranging from 1 to 49, so that from the statistical point of view the presence or absence

TABLE II. GASTRIC ACIDITY IN PATIENTS WITH MALIGNANT EXTRAGASTRIC TUMORS

TUMOR	ORGAN	ACHLORHYDRIA (0°)	HYPOCHLORHYDRIA (1 to 29°)	NORMAL ACIDITY (30 to 49°)	HYPERCHLORHYDRIA (50° OR MORE)	TOTAL
Carcinoma	Colon	9	2	5	4	20
Carcinoma	Cecum	2	2	5	1	10
Carcinoma	Rectum	5	5	2	4	16
Carcinoma	Esophagus	2	4	2	0	8
Carcinoma	Tongue	3	1	1	3	8
Carcinoma	Prostate	11	9	7	3	30
Carcinoma	Bladder	1	3	2	3	9
Carcinoma	Breast	13	5	6	5	29
Carcinoma	Bronchus	3	2	1	1	7
Carcinoma	Larynx	2	2	1	1	6
Carcinoma	Cervix-uteri	3	2	2	2	9
Carcinoma	Skin	13	12	14	10	49
Carcinoma	Anus	0	0	0	1	1
Carcinoma	Pancreas	1	1	0	0	2
Carcinoma	Kidney	1	1	0	1	3
Carcinoma	Gall bladder	1	0	0	0	1
Carcinoma	Thyroid	1	0	2	0	3
Carcinoma	Parotid	0	1	0	0	1
Carcinoma	Jejunum	0	1	0	0	1
Lymphosarcoma	Rectum	0	0	1	0	1
Lymphoblastoma	Tongue	0	1	0	0	1
Lymphatic leucemia	------	3	2	2	1	8
Hodgkin's disease	------	0	0	0	1	1
Lymphosarcoma	Tonsillar area	0	0	0	1	1
Lymphosarcoma	Lymph gland	1	1	0	0	2
Osteogenic sarcoma	Tibia and sternum	0	0	1	1	2
Chondrosarcoma	Pelvis	0	0	0	1	1
Fibrosarcoma	Leg and back	0	2	2	0	4
Malignant melanoma	----------	2	0	3	1	6
Myelogenous leucemia	----------	3	1	0	0	4
Total		80	60	59	45	244
Total (percentage)		32.8	24.6	24.2	18.4	100

of achlorhydria and hypochlorhydria for each of the group may not be significant, but for the total group of malignant and benign extragastric tumors the statistical data are valid. The incidence of achlorhydria, hypochlorhydria, normal gastric acidity, and hyperchlorhydria for this group of extragastric malignant tumors as a whole is given in Table III. It can be seen that 80 (32.8 per cent) of the patients were achlorhydric, 60 (24.6 per cent) were hypochlorhydric, 59 (24.2 per cent) had normal gastric acidity, and 45 (18.4 per cent) had hyperchlorhydria. The average age of the group was 64 years. Forty-eight per cent were female and 52 per cent were male.

TABLE III. GASTRIC ACIDITY IN MALIGNANT EXTRAGASTRIC TUMORS

DEGREES OF FREE HCL	NO.	PER CENT	AV. AGE (YEARS)	FEMALE	PER CENT	MALE	PER CENT
Achlorhydria (0°)	80	32.8	63.8	41	52	39	48
Hypochlorhydria (1-29°)	60	24.6	65	27	45	33	55
Normal (30-49°)	59	24.2	63.7	30	50	29	50
Hyperchlorhydria (50° or more)	45	18.4	66	20	46	25	54
Total	244	100	64	118	48	126	52

TABLE IV. EXTRAGASTRIC MALIGNANCIES

NEOPLASM	AVERAGE AGE (YEARS)	ACHLORHYDRIA (PER CENT)	HYPOCHLORHYDRIA (PER CENT)
Carcinoma, skin	60	26	24
Carcinoma, colon and rectum	53	35	20
Carcinoma, prostate	73	37	30
Carcinoma, breast	59	45	17

The most common form of extragastric malignancies found were of the skin (49 patients), the colon and rectum (46 patients), prostate (30 patients), and breast (29 patients). The incidence of achlorhydria and hypochlorhydria in each of these groups was as shown in Table IV.

Benign Extragastric Neoplasms.—In the benign extragastric tumor group (Table V) 30 per cent of the patients had achlorhydria, 28 per cent had hypochlorhydria, 20 per cent had normal gastric acidity, and 22 per cent had hyperchlorhydria; the average age was 64.7 years and 45 per cent were female and 55 per cent were male. The types of benign extragastric neoplasms are given in Table VI.

TABLE V. GASTRIC ACIDITY IN BENIGN EXTRAGASTRIC TUMORS

DEGREES OF FREE HCL	NO.	PER CENT	AGE (YEARS)	FEMALE	PER CENT	MALE	PER CENT
Achlorhydria (0°)	28	30	64	13	47	15	53
Hypochlorhydria (1 to 29°)	26	28	65	9	35	17	65
Normal (30 to 49°)	18	20	63.8	9	50	9	50
Hyperchlorhydria (50°) or more	21	22	66.2	10	50	11	50
Total	93	100	64.7	41	45	52	55

TABLE VI. GASTRIC ACIDITY IN PATIENTS WITH BENIGN EXTRAGASTRIC TUMORS

TUMOR	ORGAN	ACHLORHYDRIA (0°)	HYPOCHLORHYDRIA (1 TO 29°)	NORMAL ACIDITY (30 TO 49°)	HYPERCHLORHYDRIA (50° OR MORE)	TOTAL
Adenoma	Thyroid	9	7	4	4	24
Polyposis	Large bowel	0	3	4	1	8
Benign tumors, lipoma, fibroma, dermoid and sebaceous cysts, neurofibroma, melanoma, etc.	Skin and subcutaneous tissues	6	5	3	4	18
Fibroid and polyp	Uterus	4	5	2	3	14
Cysts and fibromas	Ovaries	2	1	2	5	10
Astrocytoma	Brain	2	1	0	1	4
Cyst	Maxilla	1	1	0	1	3
Mixed tumor	Parotid	0	1	0	0	1
Adenoma	Adrenal	0	0	0	1	1
Adenoma	Pituitary	1	2	0	0	3
Papilloma	Bladder (urinary)	2	0	0	0	2
Benign melanoma	Choroid	0	0	0	1	1
Chondroma	Metatarsal bone	1	0	0	0	1
Hemangioma	Vertebra	0	0	1	0	2
Dermoid cyst	Mediastinum	0	0	2	0	2
Total		28	26	18	21	94
Total (percentage)		30	28	20	22	100

In the various subdivisions of the benign and malignant extragastric tumors where there were at least 4 patients, the only marked variation in the incidence of achlorhydria and hypochlorhydria, from the group as a whole, occurred in the patients with myelogenous leucemia where the incidence of achlorhydria was 75 per cent and hypochlorhydria 25 per cent, and in polyposis of the colon where the incidence of achlorhydria was 0 (Table VI). However, the number of cases in each of these subdivisions was small (4 patients with myelogeneous leucemia and 8 patients with colonic polyposis).

Gastric Neoplasms.—

Gastric carcinoma: In this study (Table VII) there were 57 patients with gastric carcinoma. In this group the incidence of achlorhydria, hypochlorhydria, normal gastric acidity, and hyperchlorhydria were, respectively, 85 per cent, 5 per cent, 5 per cent, and 5 per cent; the average age of the group was 62 years, and 23 per cent were female and 77 per cent were male.

TABLE VII. GASTRIC ACIDITY IN CARCINOMA OF THE STOMACH

DEGREES OF FREE HCL	NO.	PER CENT	AV. AGE (YEARS)	FEMALE	PER CENT	MALE	PER CENT
Achlorhydria (0°)	48	85	62	10	21	38	79
Hypochlorhydria (1 to 29°)	3	5	56	0	0	3	100
Normal (30 to 49°)	3	5	63.3	2	66	1	33
Hyperchlorhydria (50° or more)	3	5	68	1	33	2	66
Total	57	100	62	13	23	44	77

Benign Gastric Neoplasms.—In the benign gastric neoplasms (Table VIII) there were 13 patients with gastric polyps, all of which had achlorhydria and 2 patients with leiomyoma, one of which had achlorhydria and one hyperchlorhydria; the average age for patients with polyps and leiomyomas was 61 years, and 8 of them (54 per cent) were male and 7 (46 per cent) were female.

TABLE VIII. GASTRIC ACIDITY IN BENGIN GASTRIC TUMORS

	POLYPS		LEIOMYOMAS	
DEGREES OF FREE HCL	NO.	PER CENT	NO.	PER CENT
Achlorhydria (0°)	13*	100	1†	50
Hypochlorhydria (1 to 29°)	0	0	0	0
Normal (30 to 49°)	0	0	0	0
Hyperchlorhydria (50° or more)	0	0	1†	50
Total	13	100	2	100

*7 Males and 6 females.
†Male and 1 female.
Average age 61 years.

DISCUSSION

From this study, it is evident that the incidence of achlorhydria is high in gastric neoplasms. Eighty-five per cent of the patients with gastric carcinoma had achlorhydria and an additional 5 per cent had hypochlorhydria. Thus, 90 per cent of all patients with cancer of the stomach had either achlorhydria or hypochlorhydria. These results correspond closely to those reported by Hebbel and Gaviser.[14] They found in 175 cases of gastric carcinoma

that the incidence of achlorhydria and hypochlorhydria were, respectively, 63 per cent and 17 per cent.

In benign polyps of the stomach (Table VIII) the incidence of achlorhydria was 100 per cent. This observation has been noted by others,[15] and whether this represents a cause or an effect of the polyp is still a matter of debate. It is extremely interesting to note that a polyp even the size of a pea is associated with achlorhydria even after stimulation with three doses of ½ mg. of histamine.

Leiomyomas of the stomach (Table VIII) are not regularly associated with achlorhydria or hyperchlorhydria, as in the case of gastric polyps. In this study, of the two leiomyomas of the stomach one was associated with achlorhydria, while the other was associated with hyperchlorhydria.

The incidence of achlorhydria and hypochlorhydria is not as great in the patients with malignant extragastric tumors as compared with the individuals with gastric carcinoma. The incidence of achlorhydria and hypochlorhydria in the former group was 32.8 per cent and 24.6 per cent, respectively. These figures correspond quite closely to the incidence of achlorhydria and hypochlorhydria in a group of patients of the same age group with non-neoplastic diseases, where 36 per cent of the patients were achlorhydric and an additional 23 per cent were hypochlorhydric (Table IX).

TABLE IX. GASTRIC ACIDITY IN NON-NEOPLASTIC DISEASES

DEGREES OF FREE HCL	NO.	PER CENT	AV. AGE (YEARS)	FE-MALE	PER CENT	MALE	PER CENT
Achlorhydria (0°)	327	36	60	132	40	195	60
Hypochlorhydria (1 to 29°)	210	23	62	88	42	122	58
Normal (30 to 49°)	219	24.5	66	95	42	124	58
Hyperchlorhydria (50° or more)	150	16.5	63.4	58	40	92	60
Total	906	100	62.5	373	41	533	59

It is thus apparent from these data that the incidence of achlorhydria and hypochlorhydria in patients with extragastric malignancy is about the same as for individuals without neoplasms and probably represents the incidence of achlorhydria and hypochlorhydria after histamine stimulation for the population of the same age group [16] (average age 63.2 years) (Table X). The incidence of achlorhydria and hypochlorhyria in patients with gastric malignancies, however, is definitely increased in a significant manner over the average for the same age group. It is well known that age has a definite influence on gastric acidity. Vanzant and co-workers[16] have shown that there is increase in the incidence of achlorhydria with increase of age and a definite and a swift rise in the frequency of achlorhydria in the age groups over 40 years. In this study, the possibility of difference in the incidence of achlorhydria and hypochlorhydria in the groups with extragastric and gastric malignancies being due to difference in age levels can be dismissed, for from Tables III, V, VII, VIII, it can be readily seen that the average age for people with extragastric neoplasms (both benign and malignant) is practically the same as for the patients with gastric neoplasms, These facts establish the

TABLE X. FREQUENCY OF DEGREES OF GASTRIC ACIDITY IN DISEASE GROUPS
(Percentage of total for groups given in parentheses)

DISEASE	DEGREES OF ACIDITY								TOTAL	
	0°		1 to 29°		30 to 49°		50° or more			
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
1. Non-neoplastic	327	36	210	23	219	24.5	150	16.5	906	69
2. Extragastric Tumors										
(a) Benign	28	30	26	28	18	20	21	22	93	7.1
(b) Malignant	80	32.8	60	24.6	59	24.2	45	18.4	244	18.3
3. Gastric Tumors										
(a) Carcinoma	48	85	3	5	3	5	3	5	57	4.5
(b) Polyps	13		0		0		0		13	1
(c) Leiomyoma	1		0		0		1		2	.1
Total	497	37.8	299	22.7	299	22.7	220	16.8	1315	100

If the disease groups 1 and 2 are treated as a unit and examined statistically for uniformity in degrees of chlorhydria, it is found that the small differences in the percentages are well within the chance errors of sampling ($\times^2 = 4.97$, $P = .67$). When the gastric carcinomas (group 3) are added, however, the frequency distributions become markedly heterogenous because of this addition, as evidenced by $\times^2$ rising to 61.8 and the probability of the deviations from hemogeneity arising from chance factors alone falling to much less than one in a million. It is therefore clear that the predominance of achlorhydria among patients with gastric carcinomas is associated with this disease grouping in contrast with the other disease groupings. The remaining gastric neoplasms are too few in number to warrant their inclusion separately in this analysis.

validity of the contention that the incidence of achlorhydria and hypochlorhydria is significantly greater in patients with gastric carcinoma than in patients with extragastric malignancies or non-neoplostic disease for the same age group.

SUMMARY AND CONCLUSIONS

1. One thousand three hundred fifteen patients over the age of 50 years have been studied with respect to gastric acidity following the injection of histamine as a gastric acid stimulant.

2. Two hundred forty-four patients had malignant extragastric lesions and the incidence of achlorhydria and hypochlorhydria in this group was 32.8 per cent and 24.6 per cent, respectively.

3. The incidence of achlorhydria and hypochlorhydria in 93 patients with benign extragastric tumors was 30 per cent and 28 per cent, respectively.

4. Achlorhydria and hypochlorhydria occurred in 36 per cent and 23 per cent, respectively, of 906 patients with non-neoplastic disease.

5. Of 57 patients with gastric carcinoma, 85 per cent were achlorhydric and an additional 5 per cent were hypochlorhydric.

6. Thirteen patients with gastric polyps all had achlorhydria, while of 2 patients with leiomyoma of the stomach one had achlorhydria and the other hyperchlorhydria.

7. Achlorhydria and hypochlorhydria occurs significantly more frequently in patients with cancer of the stomach than in patients with extragastric malignancies. The incidence of achlorhydria and hypochlorhydria of the latter group is practically the same as for the individuals with non-neoplastic disease of the same age group.

8. The validity of the use of achlorhydria and hypochlorhydria as signs in the diagnosis of gastric carcinoma is established in this study.

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OSTEOMYELITIS CAUSED BY SALMONELLA PARATYPHI (BACILLUS PARATYPHOSUS A)

FREDERICK E. LUDWIG, M.D., PORT HURON, MICH.

PARATYPHOID osteomyelitis has long been regarded as a comparatively rare condition. Cases reported in the literature show that osteomyelitis from a paratyphoid B organism occurred eight times to one for paratyphoid A. Most of the cases reported in the literature have not been fatal. However, certain cases, particularly in children, may terminate fatally as those cases reported by Veal and McFetridge.[1] Seidenstein[2] reported three cases that were not of the acute type but cases that appeared spontaneously without ever having shown other symptoms as an enteritis or other Salmonella infection. Primary infection of Salmonella was not recorded in any of the three cases. Roentgenograms that are reproduced in many of the articles give a picture of typical chronic osteomyelitis with more or less localized areas of destruction involving usually one or at most two bones. Jetter,[3] however, reported a case of multiple osteomyelitis complicating a paratyphoid fever which terminated fatally. The roentgenograms illustrated in his paper show considerable massive destruction of several bones of the body. This marked destruction has been noted in the following case report.

REPORT OF CASE

A 10-year-old white girl was admitted to the hospital on Aug. 16, 1946, complaining of a terrific pain and swelling of the lower end of the left femur with involvement of the knee joint. She had a history of slipping and falling on July 4, 1946, following which she noted some pain in the left knee. Two days later she noted abdominal cramps and nausea, with one or two episodes of vomiting and one of diarrhea. The next morning, on the third day following the injury, she developed severe pain in the left femur at the lower end. She was put to bed by her family and no definitive treatment was given until six weeks later when she was seen at her home with a temperature of 100° F. A large swelling appeared at the lower end of the femur involving the popliteal space so that she was unable to flex the knee and she maintained the knee in a comparatively neutral position so that it was as comfortable as possible. On August 17, a blood culture was taken and many gram-positive diplococci were found. Treatment was started prior to the report of the blood culture with 50,000 units of penicillin being given every four hours day and night. The urine examination was negative; the blood count on August 17, was 3,560,000 red cells, 69 per cent hemoglobin, 10,400 white cells, 34 per cent lymphocytes, 66 per cent neutrophiles, 56 per cent filamented, 10 per cent nonfilamented. Roentgenograms at this time disclosed (see Fig. 1) marked destruction of the entire lower end of the femur with obvious new development of bone; the destruction continuing up the shaft to the middle portion of the shaft. There was what appeared to be a large mass of undetermined nature in the politeal space.

In spite of the positive blood culture and the roentgenographic findings, it was thought that this might be an osteogenic sarcoma with a secondary infection of an osteomyelitis. The temperature under penicillin receded from 100.4° F. down to daily swings of approximately one degree. Other doctors who saw the x-ray pictures in consultation concurred in the diagnosis of an acute osteomyelitis or the possibility of an osteogenic sarcoma. On August 22, operative exploration of the infected area was undertaken with a frozen section to determine the nature of the infected condition. Preparations were made for high amputa-

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tion should this have been an osteogenic sarcoma. The frozen section proved the condition to be that of an osteomyelitis with many sequestra and much early bone formation, this accounting for its appearance as an osteogenic sarcoma. Just posterior to the lower end of the femur was a large abscess about the size of a small grapefruit. This was filled with necrotic tissue, pus, and pieces of bone. The bone was saucerized widely and curetted out with large curettes. All of the material that could be easily removed was removed from the wound. A petroleum jelly pack was left in the femur and rubber drains were inserted into the large abscess in the popliteal space. The leg was then dressed with petrolatum gauze and placed in a plaster cast hip spica to afford complete immobilization.

A culture was taken from the left femur and no organisms were found on direct smear. However, the culture recovered many cocci in clumps after twenty-four hours; the cocci grew so profusely that they covered the culture medium completely.

Two whole blood transfusions were given; one the day of the operation and one the day following it, and penicillin was continued at 50,000 units every four hours. The patient

A. *B.*

Fig. 1, *A* and *B*.—Anteroposterior and lateral views of the left femur taken on Aug. 14, 1946. These views show the extreme damage to the lower third of the femur with sequestra being formed and with an unusual rounded mass in the popliteal space extending up the shaft of the femur. There is also evidence here of much boney reaction and what appears to be osteogenesis in many areas along the bone. Also, there are several areas where the shaft has been completely opened by the infection.

apparently recovered with considerable rapidity for a few days. The two days following the operative procedure the temperature went to 100.6° F. Following that the temperature remained from 99 to 99.6° F., never going entirely to normal.

On August 27, another blood culture was taken, the results of which were found to be more cocci in clumps. On September 2, an additional blood culture was reported negative in twenty-four hours. On forty-eight hours gram-negative bacilli which were mobile were recovered. These were thought to be a contaminant so the blood culture was repeated. This blood culture also showed the gram-negative bacilli. They were traced down and found to be paratyphoid A by fermentation and biochemical reactions and by specific antiserum agglutinations. On September 12, the blood culture was repeated again because we could hardly believe our findings. Again the blood culture was positive for a gram-negative bacillus and again was proved to be paratyphoid A. On September 9, the cast was removed and the dressings changed with removal of the petrolatum gauze and the drains in the popliteal space.

A. *B.*

Fig. 2, *A* and *B*.—Anteroposterior and lateral views of the lower third of the left femur taken in December, 1946, showing the large opening in the shaft of the femur which has begun to fill in, and showing much improvement in the infected area of the lower third of the femur. The bony structure is beginning to resume its normal structure. There are, however, still evidences of periosteal reaction in the shaft and also reaction about the damaged areas in the lower thirds of the bone. It is impossible from these x-ray views to determine the exact extent of any damage to the epiphysis of the femur. However, from comparison with the first figure, it is probable that there has been damage to the medial epiphysis.

New gauze was placed in the wound and the plaster cast reapplied. Penicillin was continued all through this procedure. On September 18, penicillin was discontinued because it had no more effect on the gram-negative organisms found in the blood stream. This was a total of thirty-one days of penicillin therapy at the rate of 50,000 units every four hours.

Because we were able repeatedly to isolate this gram-negative bacillus, paratyphoid A, we decided to use streptomycin, which became available on September 20. The streptomycin was started on September 30 and given at the rate of 300 mg. every three hours for ten days. This was considered as a very large dose for a child of 10 years, however, we felt that with a positive gram-negative blood stream infection the maximum dose should be given. After eight days of treatment with streptomycin, a fine papular rash developed on both arms. On

Fig. 3.—This is a view taken in December, 1947, showing an anteroposterior view of both the right and the left knees. This shows the final result, there being a 5 per cent greater valgus deformity on the left knee as compared to the right knee. The child is now fully weight-bearing and the end result of this marked osteomyelitis has been an adequate functioning knee rather than an amputated leg.

this date another blood culture was taken and it was found to be negative for twenty-four, forty-eight, and seventy-two hours. The streptomycin, however, was continued to complete the ten days' treatment. Before treatment was stopped, there were more extensive eruptions on the arms, the chest, and the legs. There were no other symptoms of streptomycin sensitivity such as ringing of the ears, aphasia, vertigo, nausea, or vomiting.

Repeated x-ray views of the femur were made during the changes of the cast and it was found that there was no improvement in the roentgenograms until after the streptomycin therapy. By Feb. 15, 1947, there was some filling in of the osteomyelitis defect and the texture of the bone appeared more solid. Further radiographic studies taken on May 16, and at three-month intervals from that time on, show a continued improvement in the shaft of the left femur (see Fig. 2).

After one year's treatment in a plaster cast with complete immobilization, the cast was removed and the child allowed up on crutches. The skin lesion had been healed completely at the time of cessation of streptomycin therapy. There was no additional infection either from gram-negative or gram-positive organisms following the thirty-one days of penicillin and the ten days of streptomycin therapy. In August, 1947, it was found that the left leg was shortened one and one-half inches as compared with the length of the right leg. It was felt at this time that probably the epiphysis had been partitally destroyed at the lower end of the femur, especially the medial aspect of the femur. There was a 16 degree valgus deformity at the knee at this time. By October, this had not improved and a lift with an elevated heel and sole was made for the left foot. This compensated for one-half of the shortening and made her more comfortable and improved the gait. She was now allowed to walk on the leg with care and with the aid of crutches, should she wish to make any long trips. A further check in December, 1947, showed a great improvement in the length of the leg, a great improvement in the amount of calcium deposited in the affected area, and improvement in the vulgus deformity at the knee.

In December, the valgus deformity on the right leg (the good leg) was 6 degrees. The valgus deformity on the affected leg was 11 degrees, an improvement of 5 degrees over the measurements made in October, 1947. The leg had grown in length so that it was but one inch shorter than the right leg. Radiographic examination at that time showed a femur that appeared almost within normal limits, although evidences of the infection showed in the lower one-half of the bone and in the roughness seen on both antero-posterior and lateral views (Fig. 3).

DISCUSSION

It is generally considered that a mixed infection such as a coccus form and a bacillary form seldom, if ever, attack a bone simultaneously in a primary osteomyelitis. This, I believe, is a case of mixed infection in which there were two organisms involved in causing the primary lesion. It is probable that we would not have identified the two organisms were it not for the selective nature of penicillin in treating gram-negative organisms. We were able to clear the gram-positive organisms from the blood stream with the penicillin by its extended use for thirty-one days. During all of this time there was no effect on the gram-negative organisms which did not respond and which continually grew from all of the blood cultures in spite of the use of penicillin. The operative wound and the radiographic findings confirmed the presence of some additional infection other than the coccus form. The operative site did not heal or show evidences of healing under the use of the penicillin. It did show rapid closure and rapid healing after the streptomycin was used.

According to Veal and McFetridge,[1] the onset of a paratyphoid osteomyelitis, whether it is acute or subacute, seldom has the same severity as that of a pyogenic infection. In view of this, it is entirely possible that this case was primarily one of a paratyphoid A infection with a secondary coccus invasion of the bone when the patient's resistance had reached a low ebb. This child did not have a great deal of pain until after she had been disabled for about two weeks. Then she began having much more severe pain, which would mark the time when the pyogenic infection invaded the osteolytic lesion.

This case demonstrates the excellent value of penicillin for gram-positive organisms and of streptomycin for gram-negative organisms. It must be remarked here that both penicillin and streptomycin should be used in adequate amounts. Many of the failures in therapy of osteomyelitis, as in other conditions, come from the fact that not enough of the bacterial inhibitants are used from the very first. Other failures are due to stopping the drug too soon. It is true that paratyphoid organisms are about as sensitive to streptomycin as any organism except tularemia. It is my feeling that the penicillin should be used in doses not smaller than 50,000 units every four hours in any case of severe infection. With the streptomycin I feel that it should be used to the patient's tolerance immediately, keeping a close watch on the sensitivity reactions, especially ringing in the ears, vertigo, nausea, and possible vomiting. Skin manifestations, similar to the ones seen in this case, are of least importance, while ringing of the ears is the most important indication for discontinuing its use.

This case also demonstrates the well-known fact that osteomyelitis, whatever the causative agent, is still a very difficult disease to treat. This patient is making a good recovery and it is probable that the long extended immobilization had considerable value in maintaining the good work of the penicillin and the streptomycin. There is no reason in osteomyelitis to discontinue the use of open drainage, saucerization of the bone, and packing with petrolatum gauze, even though we have penicillin and streptomycin as very good bacteriostatic agents. It is probable that the blood transfusions given this child aided materially in controlling the more chronic gram-negative infection of *Bacillus paratyphosus A*.

It is probable that there have been other cases of mixed infection in osteomyelitis. It was possible to identify both organisms because of the selective action of the therapeutic agents used. Usually the coccus forms obliterate all other growth on a culture. That was true early in this case. However, with the history of enteritis for two days at the onset of this condition, I feel that the primary cause was *Bacillus paratyphoid A*. The reports in the literature concerning Salmonella infections causing osteomyelitis include the sixteen reported by Weaver, two by Veal and McFetridge, one by Jetter, three by Seidenstein, one by Krauss, a case of Salmonella infection involving the knee joint by Vinke and Downing, one by Gottche, one by Kulowski, two by Ritter and Bochner, and one by Weaver and Sherwood, making the total of twenty-eight cases. Of this group there are only four that have been definitely proved

as paratyphoid A, making the ratio of paratyphoid A osteomyelitis 1 to 6 for other Salmonella osteomyelitis cases. Any osteomyelitis caused by Salmonella infections can be considered an unusual occurrence.

CONCLUSION

Identification of the *Staphlococcus aureus* was made by repeated growth of the culture on plates. The organ maintained its characteristics of yellowish color and colony formation.

Identification of the paratyphoid A was done through fermentation reactions using first the fermentation of the carbohydrates, dextrose, lactose, saccharose, maltose, and mannitol. The results of these tests located this organ in the paratyphoid group. Further studies were made with Russell's media and Kliegler's media. The organ produced no change on the slant and produced a yellowish butt with gas formation in Kliegler's media.

Following these bacteriologic studies agglutination of the organism was done and it was found that there was positive agglutination with paratyphoid A in dilutions up to 1:60 and 1:20. There were no agglutinations with paratyphoid B agglutinins.

I should like to express my thanks to Dr. E. W. Meredith and Dr. D. W. Patterson for the radiographic work and to Dr. W. E. B. Hall for the laboratory and the pathologic work involved in this case.

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Case Reports

PRIMARY RESECTION OF GANGRENOUS ILEUM WITH ANASTOMOSIS AND SURVIVAL IN A NINETEEN-DAY-OLD INFANT

A Case Report

Ivan D. Baronofsky, M.D., and Lloyd Nelson, M.D., Minneapolis, Minn.

(From the Departments of Surgery and Pediatrics, University of Minnesota Hospitals)

THE management of strangulating gangrenous small bowel obstruction in early infancy has been a problem for many years. In their book, Ladd and Gross[1] stated that in babies under 1 year of age, the mortality of resection for gangrenous intussusception runs extremely high, averaging 75 per cent or more. In their series of eighteen cases wherein resection was combined with anastomosis, only three patients recovered. In congenital atresia of the intestine and colon, where successfully treated patients are still rarely described in the medical literature, they reported seven successful cases out of fifty-two of various anastomotic procedures. When one realizes that almost all of these patients are within the first week of life, the significance of this achievement becomes greater. More recently Dennis[2] has reported the successful use of resection and primary anastomosis in nine cases of gangrenous or non-reducible intussusceptions in children. The youngest child in this series was 39 days old, the oldest being 9 years.

At the University of Minnesota Hospitals, the use of single-layer anastomosis over clamps as advocated by Wangensteen has been the procedure of choice. He has also advocated the use of aseptic decompression and primary anastomosis in selected cases of small bowel obstruction.[3] The advantages of the "long tube" intubation of Miller and Abbott as an adjuvant in intestinal obstruction are obvious. However, the time lost in the placement of this tube in the small bowel precludes its use as the sole therapy in obstructions of a strangulating nature.

It is with this in mind that the following case of successful resection and primary end-to-end anastomosis of a strangulated gangrenous loop of bowel in a 19-day-old infant is reported.

CASE REPORT

G. B. (U. H. No. 790426), an 18-day-old white male infant, was admitted to the University of Minnesota Hospitals at 9 A.M. of June 20, 1948. About 2 A.M. on the morning of June 19, 1948, following the 2 A.M. feeding, the child began to grunt and cry as if in pain. The attacks were repeated every five to ten minutes and lasted for about two hours. Holding the child seemed to quiet him. For the next two feedings the infant took very little and whatever was taken was regurgitated. After that he remained somewhat quieter, crying only at infrequent intervals.

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The bowel movements which had previously numbered four to five per day, had decreased to one small one on the day previous to admission. At 2 A.M. on the day of admission the mother noted that the infant had passed a tarry stool with two or three bright red clots. At two- to three-hour intervals the infant seemed to have colicky pain lasting one to two minutes.

The child had been born following a normal pregnancy without complications. Labor was of ten hours' duration. Physiologic icterus was present for two weeks. Physical examination revealed a well-developed, well-nourished infant, crying out as if in pain. The chest was clear and there were no abnormalities of the heart. The abdomen was slightly distended, somewhat rigid, and tympanitic. No definite masses could be felt. Bowel sounds were increased in pitch and frequency, suggestive of a mechanical obstruction. In the left inguinal area there was a firm, somewhat indurated mass, which when palpated caused the infant to cry. Both testicles were in the scrotum.

On rectal examination, a somewhat indurated mass could be felt just to the left of the midline. On removing the finger, small fresh blood clots were noted.

Laboratory Data.—The urine was normal. The hemoglobin was 13.4 Gm.; the leucocytes numbered 15,000 per c.mm. The plasma chlorides were 561.

The diagnosis at the time rested between a strangulated inguinal hernia and an intussusception.

*X-ray Findings.**—A scout film of the abdomen revealed a rather marked distention of small bowel loops throughout most of the abdomen with no definite gas pattern recognized in colon loops. There was also considerable solid fecal material mixed with gas but it could not be determined whether this was in colon or small bowel. The appearance suggested a mechanical obstruction of the small bowel although the possibility of an ileus with impacted fecal material in the colon could not be excluded.

Barium Enema.—Barium mixture was run into the colon under very low pressure and a collapsed colon of normal length and in normal position was filled. This examination demonstrated that the large collections of solid fecal material mixed with gas noted in these films were in the small bowel proximal to the colon. There was no evidence of intussusception.

Operation.—With an intravenous needle in place, the operation was begun about thirty-five hours after the initial attack. The initial incision paralleled the left inguinal ligament. It was our thought at the time to remove the sac and bowel in toto without entering the sac (Dennis and Varco[4]). However, in dissecting down through the tissues around the sac, the contents of the sac dropped back into the peritoneal cavity. An additional incision was then made extending from the middle of the initial incision horizontally and to the right. This was extended down to and into the peritoneal cavity.

When the peritoneal cavity was entered the bowel, which was tremendously distended, eviscerated. This hampered the procedure tremendously and, therefore, an aseptic decompression was performed. This was done first simply by tapping the bowel with a 15 gauge needle and then again by the method described by Wangensteen. This decompressed the bowel considerably and an attempt was made to replace the bowel within the abdomen. At this point, difficulty with the anesthesia made it virtually impossible to do this. The pressure of the edges of the abdominal wound against the mesenteric vessels, especially the veins, caused some subserous hematoma formation in parts of the bowel, which was of some worry but little consequence.

As soon as the anesthesia was readjusted, the operation was continued. A quick examination of the bowel revealed a black gangrenous segment of about 10 cm. in length and located about 3 cm. from the ileocecal junction. It was decided to perform an anastomosis of the ileum to the ascending colon, after excising the involved ileum together with the cecum and appendix. An end-to-end aseptic anastomosis of ileum to the ascending colon was made with one row of Lembert sutures. The mesenteries were then opposed and sutured together.

The inguinal hernia was then repaired simply by closing the neck of the sac from inside the abdomen. The abdominal wall was then closed with interrupted silk sutures.

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*Interpreted by Dr. Herbert M. Stauffer.

In retrospect, the most difficult part of the entire procedure was our inability to keep the child at a plane of anesthesia wherein straining and, thereby, evisceration could be avoided.

Postoperative Course.—The postoperative course was remarkably uneventful. The infant had a bowel movement on the first postoperative day and continued having three to five movements daily thereafter. Melena which was present at first soon disappeared. The child was discharged on normal feedings on the eleventh postoperative day.

*Pathologic Report.**—The gross specimen of the terminal ileum and cecum weighed 15 Gm. A loop of bowel measured 10 cm. in length and 12 mm. in diameter. There was an area of gangrene, 4 cm. in length. The line of resection came to within 1 cm. of this area of gangrene at the nearest point. The terminal ileum and cecum were received in one piece. The terminal ileum measured 3 cm. in length and 7 mm. in diameter, the cecum 2.5 cm. in length and 10 mm. in diameter. The appendix measured 3.5 cm. in length and 3 mm. in diameter. No change was noted in this piece of the specimen.

Microscopic section of the loop of bowel which appeared grossly to be gangrenous showed extensive hemorrhage involving the serosa and muscularis. The mucosa appeared to be quite well preserved. The muscularis in some areas of the bowel was almost completely absent. The mesenteric vessels were congested with red blood cells. The appendix showed no change.

Conclusion.—Strangulated bowel, early gangrene.

Follow-up.—When last seen, one month after surgery, the child was normal in every respect. He had gained 5½ pounds.

SUMMARY

A case of primary resection of gangrenous ileum with anastomosis and survival in a 19-day-old infant is presented. The cause of the strangulation was an inguinal hernia.

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*By Dr. W. W. Walker.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

PRIMARY TERATOMAS OF THE LATERAL RETROPERITONEAL SPACES

LOUIS T. PALUMBO, M.D.,* KENNETH R. CROSS, M.D.,† ALFRED N. SMITH, M.D.,* AND ALBERT A. BARONAS, M.D.,† DES MOINES, IOWA

IN ADDITION to reporting a case of a primary teratoma of the left lateral retroperitoneal space successfully treated, we will present a review and analysis of the literature available on this subject up to 1948. In the fifth-seven cases reviewed, the diagnosis was established by the pathologic examination of surgical or autopsy specimens. This review will include briefly the historical background, the histogenesis, and the pathologic anatomy of this neoplasm. The over-all incidence and the distribution of cases according to age and sex will be presented. The symptoms and signs, treatment, and prognosis in these cases will be reviewed. This information may thus clarify the concept of an entity which is seldom discussed in medical reference volumes.

HISTORICAL

Pemberton and Whitlock[18] credit Morgagni with the first description of a retroperitoneal tumor in 1761. Tumors in this location, unrelated by origin to adjacent organs, were shown to exist by Lobstein[14] in 1829. The demonstration of a primary teratoma awaited Dickinson's[2] case in 1871. This is the case that appears in association with the name Howship in several instances in the literature. This is mentioned to avoid confusion, for the surgeon's name was W. Howship Dickinson.

HISTOGENESIS

We have no new theory relative to the origin of these tumors, nor is it our intent to prove or disprove existing theories. The most popular concepts at present center about Speman's[20] theory of embryonic primary organizers and their influence, or lack of influence, on the migration and growth of embryonic tissues. It is believed that the cells which escape organizer influence are related to the invaginating primitive streak since, with few exceptions, teratomas arise in an immediately preaxial median or paramedian location. Hansmann and Budd[12] incriminated urogenital arrests as the site of origin. There is general agreement, however, as to their congenital nature and their origin from embryonic pluripotential cells. Their subsequent growth is not under the orderly

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*From the Department of Surgery, Veterans Administration Hospital.

†From the Department of Pathology, Veterans Administration Hospital.

supervision of forces that maintain other tissues in a state of equilibrium. They are truly misdirected cells unleashed to their own devices and therefore dangerous. Needham,[17] Hamilton,[11] and Willis[23] emphasized their belief that teratomas should no longer be considered as incomplete fetuses as has been commonly done.

ANATOMY AND PATHOLOGY

The retroperitoneal space is a potential space located between the posterior parietal peritoneal wall and the anterior aspect of the posterior body wall. Its cephalic limit is the diaphragm and its attachments to the body wall. The pelvic diaphragm forms its caudal limits. Laterally the boundaries correspond to the lateral borders of the ascending and descending colon and an imaginary projection of these lines in a sagittal plane. In defining the lateral retroperitoneal area, Witzel[21] put the medial boundaries at the vertebral column and the inferior boundaries at the linea terminalis or the white line of the pelvis. This concept of the lateral retroperitoneal space is especially convenient from a clinical standpoint as sacral teratomas are excluded.

The term "primary" teratoma refers specifically to a teratoma arising independently and not from adjacent organs or structures. Metastatic tumors are also excluded by the term. A teratoma is characterized by Willis[23] as being a "true tumor or neoplasm composed of multiple tissues of kinds foreign to the part in which it arises." By the designation "true," he eliminates parasitic fetuses and heterotopic accessory organoid tissue. This is based upon the observation that a parasitic fetus is a quiescent malformation. Accessory or heterotopic organoid tissue is a coordinated orderly growth coetaneous with surrounding tissue—neoplastic qualities are missing. It is admitted that well-differentiated teratomas do have mature, adult tissue in some instances. This does not imply, however, that it is an orderly coetaneous growth. We have found no record of a primary retroperitoneal teratoma being found incidentally at necropsy. It would not be surprising should one be found. In a fatal case, reported by Hansmann and Budd,[12] the patient, a man 51 years of age, gave a history of a tender mass in the left upper abdominal quadrant at the age of 4 years. He succumbed to an infected teratoma in the left upper quadrant forty-seven years later, although the original mass had subsided forty-six years previously. Therefore, the true tumor characteristics of Willis[23] are borne out by our findings that after an unpredictable period of time retroperitoneal teratomas will become of clinical importance as a result of their growth. They are not subject to the regulating and restricting influences that the body exerts upon its normal tissues.

Embryomas and mixed tumors are differentiated by Willis[23] on the grounds that they represent tumors of tissues indigenous to an organ or region.

Simple dermoid cysts are differentiated on the basis of the lack of multiplicity of tissues. The findings of Pick and Wilms, mentioned by Ewing,[5] on the high incidence of tissue multiplicity in the so-called dermoid cysts when thoroughly examined should be kept in mind. For this reason we have been adverse to the use of the ubiquitous term "dermoid cyst."

We have made no attempt to classify the reported cases as to whether they were cystic or solid, for practically all teratomas show a relative amount of both features unless obliterated by carcinomatous or sarcomatous changes.

Of the fifty-eight cases, the record of which we have compiled in Table I, in which there were reasonably acceptable pathologic examinations, there were six cases in which malignant degeneration was present, or an incidence of 10 per cent. In Mecray's case,[16] the patient developed local recurrence and metastasis despite the fact that no evidence of malignancy was found in the teratoma at the time of removal. Watanabe's patient[24] showed carcinomatous metastasis at the age of 23 months. Follow-up studies on most cases were poor and it may be assumed that the incidence of malignancy is higher than we have stated. Also, the microscopic data on many cases were hard to evaluate. Teratomas differ in their malignant tendencies depending upon their location, as pointed out by Ewing.[5] Our statistics should not be compared to those dealing with teratomas of other sites.

The largest teratoma reported in this region weighed twenty-six pounds and was successfully removed by Gordon.[10]

In general, these neoplasms occurred in a ratio of 2:1 in the left side. Accurate determination of the point of origin was not always possible.

INCIDENCE

Evaluation of the incidence of this neoplasm was difficult because no large series has been reported from a single source. In 301 cases of malignant tumors in children, Farber[6] reported one case of retroperitoneal teratoid tumor. Donnelly[3] reported two teratomas in 95 consecutive primary retroperitoneal tumors in all ages. This series covered a twenty-year period and represented an approximate incidence of one case per 170,000 hospital admissions.[4] Donnelly[3] further estimated that there were 500 primary retroperitoneal tumors reported up to 1946. Of our collected cases 55 correspond to that time limit which indicates that 11 per cent of primary retroperitoneal tumors are teratomas. In the series of retroperitoneal tumors reported by Frank,[7] 9.3 per cent were teratomas. Gobell[9] collected 80 retroperitoneal tumors, 5 of which fulfilled the requirements of primary retroperitoneal teratomas.

We consider 58 cases, which includes our own, as bona fide primary retroperitoneal teratomas. We were unable to verify pathologically the two cases of Irna and Baljasav reported by Mecray and Frazier.[16] The case reported by Fuller and Jagger[8] did not meet the requirements in that the neoplasm did not originate in the lateral retroperitoneal space. Judd and Fulcher[3] gave no pathologic reports on their two cases. For these reasons, these five cases were dropped from consideration.

AGE

The average age of the reported cases at the time of the diagnosis was 13 years. Fifty-five per cent of these were in the first decade and 30 per cent were diagnosed during the first year of life. Ten per cent occurred in the second decade, while a secondary peak was noted in the third decade with an incidence of 25 per cent. Only 10 per cent occurred after the age of thirty. The oldest individual, reported by Gobell,[9] was 53 years of age.

TABLE I. CASES OF RETROPERITONEAL TERATOMA REPORTED IN LITERATURE

AUTHOR	SEX	AGE	LOCATION	OPERATED	RESULT	SYMPTOMS
Arnheim[1]	F	3 mo.	Left	Yes	Lived	Abdominal enlargement; W.B.C. 16,000; constipation
Bauer, A.: Beitr. z. klin. Chir. **75**: 226, 1911	M	14 yr.	Left	Yes	Died	Abdominal mass, pain, weight loss, dilated veins
Brouha, A.: Rev. de gynec e d'obst. **6**: 401, 1902	F	26 yr.	Left	Yes	Died	?
Budde, W.: Beitr. z. path. Anat. **75**: 357, 1926, quoted by Arnheim[1]	M	2 mo.	Left and right	Yes	Died	Abdominal mass, dilated veins, vomiting
Bardenheurer, B.: quoted by Gobell[9]	F	17 yr.	Right	Yes	Died	Abdominal mass
Campbell, M. J.: J. Urol. **29**: 677, 1933	M	6 mo.	L.L.Q.	Yes	Lived	Abdominal mass, constipation, weight loss
Dickinson[2]	F	2 yr.	L.L.Q.	No	Died	Abdominal mass
Donnelly[3]	?	?	?	Yes	?	?
Durante, G., and David, C.: Bull. et mém. Soc. anat. de Paris **82**: 328, 1907, quoted by Arnheim[1]	?	Neonatal	Left and right	No	Died	?
Eerland, L. D.: Nederl. tijdschr. v. verlosk. en gynaec. **41**: 56, 1938, quoted by Arnheim[1]	F	8 mo.	Left and right	Yes	Lived	Abdominal mass
Froboese, C.: Frankfurt. Ztschr. f. Path. **43**: 222, 1932, quoted by Arnheim[1]	F	15 mo.	R.U.Q.	No	Died	Abdominal enlargement
Feldmann, I.: Centralbl. f. allg. Path. u. path. Anat. **48**: 321, 1930*	M	20 yr.	R.U.Q.	No	Died	Abdominal mass
Gale, C., and Willis, R.: J. Path. & Bact. **56**: 403, 1944	F	13 yr.	Left and right	Yes	Lived	Abdominal mass
Gobell[9]*	F	53 yr.	Left	Yes	Died; metastasis	Abdominal mass, pain
Gordon[10]	F	50 yr.	Right	Yes	Lived	Abdominal mass
Gross: Ass. franç. de chir. Proc.-verb. **7**: 666, 1893, quoted by Mecray and Frazier[16]	F	26 yr.	R.U.Q.	Yes	Lived	Abdominal mass
Gude, H. W. W.: Greifswald, 1898, F. W. Kunike, quoted by Gobell[9]	M	9 yr.	L.L.Q.	Yes	Died	Abdominal mass
Hansmann and Budd[12]	M	51 yr.	L.U.Q.	Yes	Died	Lumbar pain, fever
Hosmer, H.: Boston M. & S. J. **102**: 61, 1880	F	8 mo.	Right	No	Died	Abdominal mass, fever, weight loss
Johnson, R., and Lawrence, T.: Proc. Roy. Soc. Med. **3**: 43, 1909.	M	3 yr.	Left	Yes	Died	Abdominal mass
Kaneko, Y.: Gann **18**: 77, 1924, quoted by Mecray[16]	M	10 mo.	Left and right	No	Died	Abdominal mass

*Malignant.

TABLE I—CONT'D

AUTHOR	SEX	AGE	LOCATION	OPERATED	RESULT	SYMPTOMS
Kolb, K.: quoted by Portugal	F	7 wk.	Left	No	Died	Abdominal mass, dilated veins
Kon: J. Tokio M. Soc. 16: 1904, quoted by Terasako	M	9 yr.	Left	Yes	Died	Abdominal mass
Kostitch, M.: Compt. rend. Soc. de biol. 90: 1081, 1924	M	22 yr.	L.U.Q.	Yes	Died	Abdominal mass, pain
Kuznetsoff, D. D.: Med. pribav. k morsk. sborniku, p. 101, 1910	M	4 mo.	Left	Yes	Died	Abdominal mass, constipation
Landivar, A. F., and Iparraguirre, C. A.: Bol. y trab., Soc. de cir. de Buenos Aires 19: 837, 1935, quoted by Mecray[16]	M	45 yr.	L.U.Q.	Yes	Lived	Abdominal
Lexer, E.: Arch. f. klin. Chir. 61: 648, 1900	F	11 yr.	L.U.Q.	Yes	Lived	Abdominal mass, pain, fever
Lightwood, R.: Proc. Roy. Soc. Med. 25: 1736, 1932	F	7 wk.	R.U.Q.	Yes	Lived	Abdominal enlargement, mass, constipation
Lundblad, O.: Acta chir. Scandinav. 72: 174, 1932	F	4 yr.	?	Yes	Died	?
Lundblad, O.: ibid.	F	4 yr.	?	Yes	Lived	?
Lundblad, O.: ibid.	F	25 yr.	?	Yes	Died	?
Marchand, F.: Breslau aerztl. Ztschr. 3: 251, 1881, quoted by Portugal	F	35 yr.	L.U.Q.	Yes	Died	?
Maydl[15]	F	?	?	Yes	?	?
Mecray and Frazier[16]*	M	29 yr.	R.U.Q.	Yes	Recurred; metastases	Abdominal pain; W.B.C. 15,000
Meckel, J. F.: Handb. d. path. anatomie, Leipzig, Reclam. 1812, quoted by Portugal	?	?	L.U.Q.	No	Died	?
Nicholson, C. M.: Am. J. Clin. M. 13: 343, 1906*	M	21 yr.	R.U.Q.	Yes	Died	Abdominal mass, pain, vomiting
Nicholson, G. W. P.: Guy's Hosp. Rep. 85: 379, 1935	F	7 mo.	Right	Yes	Lived	Abdominal mass, pain
Nicholson, G. W. P.: J. Path. & Bact. 32: 365, 1929	F	4 mo.	L.U.Q.	No	Died	?
O'Leary, C. M., and Halpert, B.: SURGERY 21: 194, 1947	F	15 mo.	R.U.Q.	Yes	Lived	Abdominal enlargement and mass
Paltauf, R.: Centralbl. f. allg. Path. 53: 136, 1931	F	5 mo.	Left	No	Died	Abdominal mass
Pilliet, A.: Bull. Soc. anat. de Par. 63: 875, 1888, quoted by Mecray[16]*	F	24 yr.	Left and right	Yes	Died; sarcoma	Abdominal mass
Portugal, J. E.: Thèsé de Bordeaux, No. 71, 1919	F	17 yr.	L.U.Q.	Yes	Died	Abdominal mass, pain, vomiting
Roux, P. J.: Compt. rend. Soc. de biol. 3: 291, 1836, quoted by Mecray[16]	F	25 yr.	Left and right	No	Died	Abdominal mass, uremia
Ruge[19]	M	27 yr.	Left	Yes	?	?

(Continued on following page.)

TABLE I—CONT'D

AUTHOR	SEX	AGE	LOCATION	OPERATED	RESULT	SYMPTOMS
Sand, R., and Lerat, P.: Bull. Acad. de. méd., Belge 26: 115, 1912, quoted by Arnheim[1]	M	15 yr.	Left	Yes	Died	Abdominal mass, fever
Schonholzer, G.: Beitr. z. path. Anat. u.z. allg. Path. 40: 349, 1906	M	2 yr.	L.U.Q.	No	Died	Abdominal mass
Seki, M.: Gann 21: 20, 1927, quoted by Mecray[16]	M	22 mo.	Left	No	Died	Abdominal mass
Smith, E., and Cochrane, W.: Canad. M.A.J. 55: 151, 1946	M	2 mo.	L.U.Q.	Yes	Lived	Abdominal enlargement and mass
Terasako, S.: Okayama-Igakkai-Zasshi 46: 435, 1934	M	3 mo.	Right	No	Died	Abdominal mass
Tillaux, M.: Gaz. d. hôp. 59: 757, 1886, quoted by Mecray[16]	F	22 yr.	L.U.Q.	Yes	Died	Abdominal mass
Trethowan, W., and Dale, J.: M.J. Australia 1: 540, 1924	F	24 yr.	R.L.Q.	Yes	Lived	Abdominal enlargement and mass
Tsuda: J. Japanese Surg. A. 21: 1920, quoted by Terasako	M	17 mo.	Left	Yes	Died	Abdominal mass
Usandizago, M., and Mayor, J.: Arch. de med., cir. y especialid. 34: 596, 1931, quoted by Mecray[16]	F	28 yr.	L.L.Q.	Yes	Lived	Abdominal pain
Watanabe[24]*	M	23 mo.	L.U.Q.	No	Died	Abdominal mass
Weier, F.: Beitr. z. Klin. Chir. 155: 125, 1932	?	18 mo.	Left and right	Yes	Lived	Abdominal mass
Willis[22]	F	9 mo.	R.L.Q.	?	Died	?
Willis[22]	F	9 wk.	R.U.Q.	Yes	Lived	Abdominal mass
Our case	M	44 yr.	L.U.Q.	Yes	Lived	Backache

SEX

The sex was not recorded in four cases. Of the remainder, 57 per cent were females and 43 per cent were males.

SYMPTOMS AND FINDINGS

Abdominal enlargement and a palpable mass are the most common findings in these cases. The symptoms are vague and not alarming until the growth of the tumor is well advanced. They are predominantly the result of pressure incident to the growth of the neoplasm. They frequently include abdominal or back pain. There are symptoms of intestinal obstruction with nausea, vomiting, constipation, and weight loss in some cases. Less frequently, the symptoms are referable to the urinary system. It is not uncommon to find dilatation and prominence of the veins of the anterior abdominal wall as collateral circulation is established. Secondary edema of the lower extremities may result. The tumor may transmit aortic pulsations. Its motility is generally limited. Occasionally, a low-grade fever has been recorded in children, but Mecray and Frazier[16] stated that fever is more common in retroperitoneal sarcomas.

DIAGNOSIS

The specific diagnosis is usually not possible preoperatively, particularly when calcific deposits cannot be seen in roentgenograms. Given a case with an abdominal mass, regardless of symptomatology unless acute, time should be taken to localize the site by means of roentgen studies of the gastrointestinal and urinary tracts. This will also give the surgeon some evaluation of the integrity and function of adjacent organs and structures and it may determine the operability of the tumor and/or the type of surgery to be performed.

Donnelly,[3] investigating primary retroperitoneal tumors of all types, stated that they are most frequent in men in a ratio of approximately 2:1 and that they occurred chiefly in the fourth and fifth decades of life. This we feel is of diagnostic significance, for, in the case of teratomas, only 5.5 per cent of the cases occur in that age group and they are slightly more common in women.

PROGNOSIS

The over-all mortality in this group was 70 per cent. Four cases (Donnelly,[3] Maydl,[15] Ruge,[19] and Willis[22] are excluded here because of insufficient data. Of the 39 cases with operation, in which the outcome was stated, the patient mortality was 54 per cent. An analysis of the cases with operation during the past ten years, which number 6 including our own, reveals that the patient mortality has been 0.

Judging from this series, 10 per cent of the teratomas may be expected to be malignant at the time of the operation. Early removal of the teratomas will be accompanied by a reduction in the number showing malignancy.

CASE REPORT

G. J., a 43-year-old white man, a truck driver, was admitted to the hospital May 11, 1948, complaining of a low backache of five weeks' duration. This began after lifting the side of a truck box which weighed approximately 300 pounds. After an x-ray examination by the referring physician, he was treated with hot baths. A lumbosacral belt was applied which gave no relief. The pain was constant and dull. It was aggravated by prolonged standing, lifting, bending, and jolting. There was periodic radiation into the right hip with extension down the lateral aspect of the thigh. There had been no numbness or paresthesia.

The patient had had a fracture of the pelvis in 1937 when he was thrown by a cyclone. Since that time he had had periodic right hip pain. For the pain he was admitted to this hospital in 1944 and 1945. On both occasions, the x-ray examination revealed slight deformity of the right pubic and ischial rami. This was interpreted as residuals of the previous fracture. The remaining past medical history was irrelevant.

Physical examination was complete. Hyperextension of the lumbar spine aggravated the pain in that area. No other abnormalities were found. Clinical laboratory examinations, including a complete blood count and hemoglobin determination, Kahn test, urinalysis, blood sugar, total plasma proteins, and nonprotein nitrogen determinations, were all within the limits of normal.

A posteroanterior roentgenogram of the chest was within normal limits. A routine study (anteroposterior and lateral) of the lumbar spine revealed no significant bony disease or injury, except for an old healed fracture of the right hemipelvis. However, in the anteroposterior projection (Fig. 1), an ovoid shadow of "eggshell" configuration was seen in the apex of the psoas shadow medial to the left kidney. At its superior pole, a small dense opaque shadow was visible which suggested a small fragment of tooth. Near the inferior

pole, an irregular calcific plaque was visible which appeared to be essentially an amorphous calcium deposit. The renal shadow was displaced somewhat cephalad and laterally. In the upright position, no fluid levels were seen, nor was the interior of the shadow reticulated or suggestive of "matted hair."

Intravenous and retrograde pyelograms were entirely within normal limits, except for slight dilatation of the left renal pelvis and displacement of the renal shadow, demonstrated in the conventional and oblique views (Figs. 2 and 3). The evidence supported the view that the lesion was retroperitoneal and undoubtedly a teratoma.

Operative Findings.—On June 7, 1948, under nitrous oxide anesthesia, the left posterior retroperitoneal space from the diaphragm to the sacral promontory was exposed through a left oblique lumbar incision utilizing the retroperitoneal approach.

Fig. 1.

Fig. 2.

Fig. 1.—Roentgenogram (anteroposterior) showing an ovoid shadow of "eggshell" configuration in apex of the psoas shadow medial to the left kidney.

Fig. 2.—Retrograde pyelogram (anteroposterior) showing lateral displacement of left kidney.

A thick-walled, smooth, fluctuant mass was found attached to the left lateral aspect of the bodies and transverse processes of the first to the fourth lumbar vertebrae. The sac measured 13 cm. in length and 6 cm. in diameter. It was buried in the fibers of the left psoas muscle and was attached, by thick fibrous strands, to this structure and to the adjoining vertebrae. The most densely adherent point was at the superior pole. It contained, in addition to fluid, a ball of hair. There were two areas of calcification in the wall. After aspiration of 150 c.c. of greenish-yellow, sebaceous material, the mass was reduced in size to facilitate its complete dissection and removal. Careful dissection was necessary to free the left genitofemoral and femoral cutaneous nerves. Bleeding was controlled by Gelfoam and Oxycel. Two Penrose drains were placed through a stab wound in the loin. The wound was closed in layers.

Surgical Pathologic Findings.—The inner surface of the cyst wall was smooth for the most part, but was rough and hemorrhagic in a few areas. It was trabeculated. At many points, there were large pores filled with cheesy material. Two small masses of hair and sebum and the two calcified masses previously described were found in the wall.

Fig. 3.—Retrograde pyelogram (oblique) showing anterior displacement of left kidney.

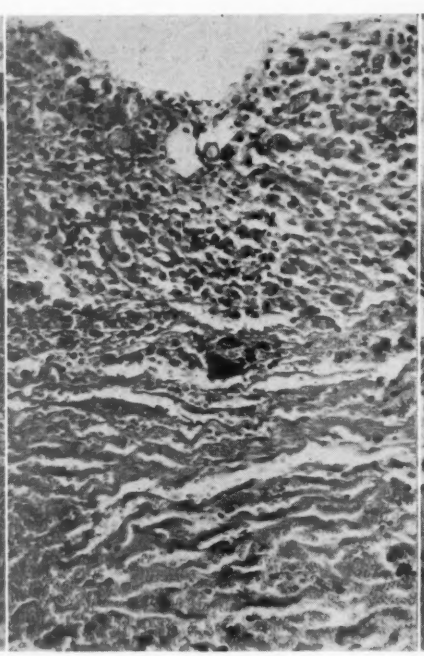

Fig. 4. Fig. 5. Fig. 6.

Fig. 4.—Hematoxylin and eosin stain (×60). Cyst wall showing squamous epithelium, hair follicle, and sebaceous glands.

Fig. 5.—Hematoxylin and eosin stain (×100). Cyst wall consisting of granulation tissue.

Fig. 6.—Hematoxylin and eosin stain (×100). Decalcified compact bone from cyst wall.

Microscopically, the lining consisted of a thin layer of squamous epithelium (Fig. 4). In the subcutaneous tissue numerous large sebaceous glands were seen. Hair follicles were present. Areas which appeared roughened and hemorrhagic were lined by granulation tissue (Fig. 5). A dense fibrous connective tissue stroma was infiltrated with lymphocytes, plasmocytes, and many large mononuclear cells. A few giant cells were seen. Both small and diffuse areas of recent hemorrhage were numerous. Peripherally, the wall was made up of scarred fat and striated muscle showing some round-cell infiltration, particularly in perivascular locations. Two large myelinated nerve trunks of normal structure were seen. Decalcified tissue revealed small areas of bone closely incorporated in the fibrous wall of the cyst (Fig. 6). Intramembranous bone formation was apparent. Some calcium salts were deposited in the fibrous tissue. No evidence of entodermal structure was found. No evidence of malignancy was apparent.

Fig. 7.—Retrograde pyelogram (anteroposterior), postoperatively, showing the left kidney in a less lateral position.

Course in Hospital.—Postoperatively, the drains were removed on the third day, the patient was ambulatory on the fourth day, and the wound healed by primary intention. On the second day there was hypesthesia along the distribution of the left genitofemoral nerve and loss of the left cremasteric reflex. On the eighth day, an erythematous, pruritic rash appeared along the distribution of the left medial femoral cutaneous nerve. This subsided by the fourteenth day. An intravenous pyelogram on the fifteenth day revealed that the left kidney had returned some distance toward the midline. The patient was discharged on the twenty-fifth postoperative day with functional impairment of the left genito-femoral nerve.

Readmission Note.—The patient was readmitted for the follow-up examination on Oct. 6, 1948, three months after discharge. He stated that the periodic discomfort in the right hip was still present. A burning pain, aggravated by heavy lifting, was present in the periumbilical area. The patient had been otherwise asymptomatic. There was an umbilical hernia present, which measured approximately 1 cm. in diameter. The neurological examination, including the lower extremities, was negative. X-ray studies of the lumbar and dorsal spine and the retrograde pyelogram (Fig. 7) revealed no abnormalities. An umbilical hernioplasty was performed on Oct. 13, 1948, with an uneventful postoperative convalescence. Again, examination of the testicles revealed no abnormalities.

SUMMARY

A review of fifty-seven primary teratomas of the lateral retroperitoneal spaces is presented. An additional case has been studied and the patient successfully treated by us. The origin of these tumors can only be theorized. In this series 10 per cent of the teratomas had undergone malignant changes. The remaining teratomas caused symptoms of pressure as their local growth encroached on surrounding organs. Commensurate with its congenital nature, the tumor manifests itself most frequently in persons of the younger age groups. A slightly higher incidence of occurrence has been found in females than in males. The left side was twice as frequently the site of origin as was the right side. The size of the growth is variable and of no benefit in differentiating teratomas from other tumors of the retroperitoneal spaces. Diagnosis can be expedited by roentgenologic evidence of bones or teeth within the tumor. When such positive objective evidence is lacking, the diagnostician is beset with the difficult problem of giving a preoperative diagnosis. By virtue of an understanding of the clinical characteristics of the individual tumor types this problem can be met. We have attempted to find clinical characteristics of diagnostic significance in these compiled cases of retroperitoneal teratomas.

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ANNOUNCEMENT

BRITISH AMERICAN EXCHANGE FELLOWSHIPS IN CANCER RESEARCH

AWARDED UPON RECOMMENDATION OF THE COMMITTEE ON GROWTH OF THE NATIONAL RESEARCH COUNCIL

British American Exchange Fellowships in Cancer Research of the American Cancer Society, awarded by the Society upon recommendation of the Committee on Growth of the National Research Council, are offered to citizens of the United States for advanced training and experience in Great Britain in specialized fields of investigation pertaining to the problem of cancer. Similar fellowships are awarded by the British Empire Cancer Campaign to British scientists for study in the United States. The Society and the Committee on Growth welcome the cooperation of universities and hospitals in making known these opportunities to suitable candidates.

FIELDS OF STUDY

These fellowships are awarded by the American Cancer Society to provide specialized training for American investigators in Great Britain where opportunities exist for study in facets of research in malignant disease not widely available in this country. Training for an equal number of young British scientists selected by the Campaign will be provided in this country. The Society, the Committee on Growth, and the British Empire Cancer Campaign believe that the training of young men and women in the many complex disciplines of modern scientific thought and techniques are fundamental to a sound approach to the problem of human cancer.

Candidates will be favored who express intention of following a career in a discipline applicable to the study of growth. In evaluating fellowship applications the Committee will keep in mind potential applicability of the proposed training program to problems of neoplastic growth in specialized scientific areas in which superior facilities exist in Great Britain.

QUALIFICATIONS OF APPLICANTS

Fellowships are open to citizens of the United States who possess the degree of Doctor of Medicine, Doctor of Philosophy, or Doctor of Science. They are intended for young men and women embarking upon a career in clinical medicine or basic research, and also for more mature candidates desiring to extend their fields of competence in these fields. Applicants must be able to demonstrate that they have qualifications necessary to pursue investigation in the fundamental sciences or in clinical medicine.

Applications should state the institution where the fellow plans to work in Great Britain; the individual under whom the fellow desires to work; what problem he intends to investigate; when he wishes to start.

CONDITIONS OF APPOINTMENT

Fellowships will be awarded for a period of one year.

The annual stipend will be £1000 ($4,020.00). An allowance of $600.00 is made for travel to the site of the fellowship in Great Britain.

University staff appointment, with teaching duties agreeable to the fellow, is permitted, provided it carries no additional salary and provided it is acceptable to the Committee on Growth, the American Cancer Society, and the British Empire Cancer Campaign. No other remunerative work will be permitted during the tenure of the fellowship.

Fellowship appointments are subject to the condition that, once accepted, they will not be vacated or the place of work changed within the period of tenure without the consent of the Committee on Growth, the American Cancer Society, and the British Empire Cancer Campaign.

TIME OF APPLICATION

Application forms for British American Exchange Fellowships in Cancer Research may be procured from and submitted at any time to the Executive Secretary of the Committee on Growth, Division of Medical Sciences, National Research Council, 2101 Constitution Ave., Washington 25, D. C. Favorable action by the Committee on Growth takes the form of a recommendation to the American Cancer Society, and is subject to approval by the Society. Fellowships will be made effective at the convenience of the institution and the fellow.